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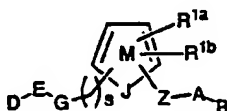
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(54) Title: NITROGEN CONTAINING HETEROAROMATICS WITH ORTHO-SUBSTITUTED P1'S AS FACTOR XA INHIBITORS



(I)

(57) Abstract: The present application describes nitrogen containing heteroaromatics with ortho-substituted P1's and derivatives thereof of Formula (I) or pharmaceutically acceptable salt or prodrug forms thereof, wherein J is N or NH and D is substituted ortho to G on E and may be CH₂NH₂, which are useful as inhibitors of factor Xa.

TITLE

Nitrogen Containing Heteroaromatics with Ortho-Substituted
P1's as Factor Xa Inhibitors

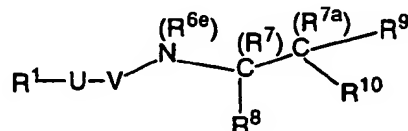
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FIELD OF THE INVENTION

This invention relates generally to nitrogen containing heteroaromatics, with ortho-substituted P1 groups, which are inhibitors of trypsin-like serine protease enzymes, especially factor Xa, pharmaceutical compositions containing the same, and methods of using the same as anticoagulant agents for treatment and prevention of thromboembolic disorders.

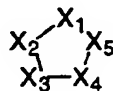
BACKGROUND OF THE INVENTION

WO 95/18111 addresses fibrinogen receptor antagonists, containing basic and acidic termini, of the formula:



wherein R¹ represents the basic termini, U is an alkylene or heteroatom linker, V may be a heterocycle, and the right hand portion of the molecule represents the acidic termini. The presently claimed compounds do not contain the acidic termini of WO 95/18111.

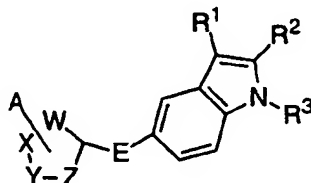
In U.S. Patent No. 5,463,071, Himmelsbach et al depict cell aggregation inhibitors which are 5-membered heterocycles of the formula:



wherein the heterocycle may be aromatic and groups A-B-C- and F-E-D- are attached to the ring system. A-B-C- can be a wide variety of substituents including a basic group attached to an aromatic ring. The F-E-D- group, however, would appear to be an acidic functionality which differs from the present

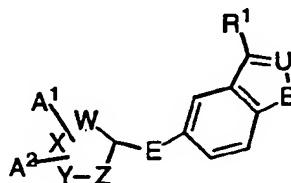
invention. Furthermore, use of these compounds as inhibitors of factor Xa is not discussed.

Baker et al, in U.S. Patent No. 5,317,103, discuss 5-HT₁ agonists which are indole substituted five-membered
 5 heteroaromatic compounds of the formula:



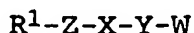
wherein R¹ may be pyrrolidine or piperidine and A may be a
 10 basic group including amino and amidino. Baker et al, however, do not indicate that A can be a substituted ring system like that contained in the presently claimed heteroaromatics.

Baker et al, in WO 94/02477, discuss 5-HT₁ agonists which
 15 are imidazoles, triazoles, or tetrazoles of the formula:



wherein R¹ represents a nitrogen containing ring system or a
 20 nitrogen substituted cyclobutane, and A may be a basic group including amino and amidino. Baker et al, however, do not indicate that A can be a substituted ring system like that contained in the presently claimed heteroaromatics.

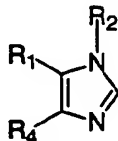
Illig et al, in WO 97/47299, illustrate amidino and
 25 guanidino heterocycle protease inhibitors of the formula:



wherein R¹ can be a substituted aryl group, Z is a two carbon
 30 linker containing at least one heteroatome, X is a heterocycle, Y is an optional linker and W is an amidino or

guanidino containing group. Compounds of this sort are not considered part of the present invention.

Jackson et al, in WO 97/32583, describe cytokine inhibitors useful for inhibiting angiogenesis. These
5 inhibitors include imidazoles of the formula:



wherein R₁ is a variety of heteroaryl groups, R₄ is phenyl, naphthyl, or a heteroaryl group, and R₂ can be a wide variety
10 of groups. Jackson et al do not teach inhibition of factor Xa. Furthermore, the imidazoles of Jackson et al are not considered part of the present invention.

Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of
15 prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of
20 prothrombinase complex (factor Xa, factor V, Ca²⁺ and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin (Elodi, S., Varadi, K.: *Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of*
25 *the complex in the amplification of blood coagulation. Thromb. Res. 1979, 15, 617-629*), inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system.

Therefore, efficacious and specific inhibitors of factor
30 Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors.

SUMMARY OF THE INVENTION

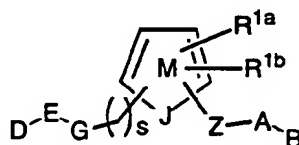
35 Accordingly, one object of the present invention is to provide novel nitrogen containing aromatic heterocycles, with

ortho-substituted P1 groups, which are useful as factor Xa inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

It is another object of the present invention to provide
 5 pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide
 10 a method for treating thromboembolic disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

15 These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula (I):

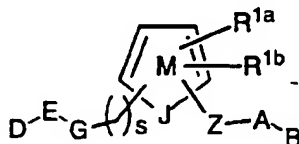


I

20 or pharmaceutically acceptable salt or prodrug forms thereof, wherein A, B, D, E, G, J, M, R^{1a}, R^{1b}, and s are defined below, are effective factor Xa inhibitors.

25 DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides novel compounds of formula I:



I

30 or a stereoisomer or pharmaceutically acceptable salt thereof, wherein;

ring M contains, in addition to J, 0-3 N atoms, provided that if M contains 2 N atoms then R^{1b} is not present and if M contains 3 N atoms then R^{1a} and R^{1b} are not present;

5 J is N or NH;

D is selected from CN, C(=NR⁸)NR⁷R⁹, NHC(=NR⁸)NR⁷R⁹, NR⁸CH(=NR⁷), C(O)NR⁷R⁸, and (CR⁸R⁹)_tNR⁷R⁸, provided that D is substituted ortho to G on E;

10

E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, and piperidinyl substituted with 1-2 R;

15

R is selected from H, Cl, F, Br, I, (CH₂)_tOR³, C₁₋₄ alkyl, OCF₃, CF₃, C(O)NR⁷R⁸, and (CR⁸R⁹)_tNR⁷R⁸;

G is absent or is selected from NHCH₂, OCH₂, and SCH₂, provided that when s is 0, then G is attached to a carbon atom on ring M;

20

Z is selected from a C₁₋₄ alkylene, (CH₂)_rO(CH₂)_r, (CH₂)_rNR³(CH₂)_r, (CH₂)_rC(O)(CH₂)_r, (CH₂)_rC(O)O(CH₂)_r, (CH₂)_rOC(O)(CH₂)_r, (CH₂)_rC(O)NR³(CH₂)_r, (CH₂)_rNR³C(O)(CH₂)_r, (CH₂)_rOC(O)O(CH₂)_r, (CH₂)_rOC(O)NR³(CH₂)_r, (CH₂)_rNR³C(O)O(CH₂)_r, (CH₂)_rNR³C(O)NR³(CH₂)_r, (CH₂)_rS(O)_p(CH₂)_r, (CH₂)_rSO₂NR³(CH₂)_r, (CH₂)_rNR³SO₂(CH₂)_r, and (CH₂)_rNR³SO₂NR³(CH₂)_r, provided that Z does not form a N-N, N-O, N-S, NCH₂N, NCH₂O, or NCH₂S bond with ring M or group A;

30

R^{1a} and R^{1b} are independently absent or selected from -(CH₂)_r-R^{1'}, -CH=CH-R^{1'}, NCH₂R^{1''}, OCH₂R^{1''}, SCH₂R^{1''}, NH(CH₂)₂(CH₂)_tR^{1'}, O(CH₂)₂(CH₂)_tR^{1'}, and S(CH₂)₂(CH₂)_tR^{1'};

35

alternatively, R^{1a} and R^{1b}, when attached to adjacent carbon atoms, together with the atoms to which they are attached form a 5-8 membered saturated, partially saturated or

unsaturated ring substituted with 0-2 R^4 and which contains from 0-2 heteroatoms selected from the group consisting of N, O, and S;

- 5 $R^{1'}$ is selected from H, C_{1-3} alkyl, F, Cl, Br, I, -CN, -CHO, $(CF_2)_rCF_3$, $(CH_2)_rOR^2$, NR^2R^{2a} , $C(O)R^{2c}$, $OC(O)R^2$, $(CF_2)_rCO_2R^{2c}$, $S(O)_pR^{2b}$, $NR^2(CH_2)_rOR^2$, $CH(=NR^{2c})NR^2R^{2a}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NHR^{2b}$, $NR^2C(O)_2R^{2a}$, $OC(O)NR^{2a}R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NR^2(CH_2)_rOR^2$, $SO_2NR^2R^{2a}$, $NR^2SO_2R^{2b}$, C_{3-6}
- 10 carbocyclic residue substituted with 0-2 R^4 , and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^4 ;
- 15 $R^{1''}$ is selected from H, $CH(CH_2OR^2)_2$, $C(O)R^{2c}$, $C(O)NR^2R^{2a}$, $S(O)R^{2b}$, $S(O)_2R^{2b}$, and $SO_2NR^2R^{2a}$;
- R^2 , at each occurrence, is selected from H, CF_3 , C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b} ,
- 20 and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b} ;
- R^{2a} , at each occurrence, is selected from H, CF_3 , C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b} ,
- 25 and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b} ;
- 30 R^{2b} , at each occurrence, is selected from CF_3 , C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b} , and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b} ;
- 35 R^{2c} , at each occurrence, is selected from CF_3 , OH, C_{1-4} alkoxy, C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b} , and 5-6 membered heterocyclic system

containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

- alternatively, R² and R^{2a} combine to form a 5 or 6 membered
5 saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;
- 10 alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1
15 additional heteroatoms selected from the group consisting of N, O, and S;

R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

- 20 R^{3a}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3b}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

- 25 R^{3c}, at each occurrence, is selected from C₁₋₄ alkyl, and phenyl;

A is selected from:

- 30 C₃₋₁₀ carbocyclic residue substituted with 0-2 R⁴, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

- 35 B is selected from:

X-Y, NR²R^{2a}, C(=NR²)NR²R^{2a}, NR²C(=NR²)NR²R^{2a}, C₃₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and

5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

- 5 X is selected from C₁₋₄ alkylene, -CR²(CR²R^{2b})(CH₂)_t-, -C(O)-, -C(=NR^{1'})-, -CR²(NR^{1'}R²)-, -CR²(OR²)-, -CR²(SR²)-, -C(O)CR²R^{2a}-, -CR²R^{2a}C(O)-, -S(O)_p-, -S(O)_pCR²R^{2a}-, -CR²R^{2a}S(O)_p-, -S(O)₂NR²-, -NR²S(O)₂-, -NR²S(O)₂CR²R^{2a}-, -CR²R^{2a}S(O)₂NR²-, -NR²S(O)₂NR²-, -C(O)NR²-, -NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-, -CR²R^{2a}C(O)NR²-, -CR²R^{2a}NR²C(O)-, -NR²C(O)O-, -OC(O)NR²-, -NR²C(O)NR²-, -NR²-, -NR²CR²R^{2a}-, -CR²R^{2a}NR²-, O, -CR²R^{2a}O-, and -OCR²R^{2a}-;
- 10
- 15 Y is selected from:
 (CH₂)_rNR²R^{2a}, provided that X-Y do not form a N-N, O-N, or S-N bond,
 C₃₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and
 5-10 membered heterocyclic system containing from 1-4
 20 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};
- R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a},
 25 (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a}, CH(=NR²)NR²R^{2a}, CH(=NS(O)₂R⁵)NR²R^{2a}, NHC(=NR²)NR²R^{2a}, C(O)NHC(=NR²)NR²R^{2a}, SO₂NR²R^{2a}, NR²SO₂NR²R^{2a}, NR²SO₂-C₁₋₄ alkyl, NR²SO₂R⁵, S(O)_pR⁵, (CF₂)_rCF₃, NCH₂R^{1'}, OCH₂R^{1'}, SCH₂R^{1'}, N(CH₂)₂(CH₂)_tR^{1'}, O(CH₂)₂(CH₂)_tR^{1'}, and
 30 S(CH₂)₂(CH₂)_tR^{1'},

alternatively, one R⁴ is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

35

R^{4a}, at each occurrence, is selected from H, =O, (CH₂)_rOR², (CH₂)_r-F, (CH₂)_r-Br, (CH₂)_r-Cl, Cl, Br, F, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b},

$C(O)NR^2R^{2a}$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$,
 $CH(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$,
 $NR^2SO_2-C_{1-4}$ alkyl, $C(O)NHSO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$,
 and $(CF_2)_rCF_3$;

5

alternatively, one R^{4a} is a 5-6 membered aromatic heterocycle
 containing from 1-4 heteroatoms selected from the group
 consisting of N, O, and S substituted with 0-1 R^5 ;

10 R^{4b} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, F,
 Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^3R^{3a}$,
 $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$,
 $NR^3C(O)NR^3R^{3a}$, $CH(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$,
 $NR^3SO_2NR^3R^{3a}$, $NR^3SO_2-C_{1-4}$ alkyl, $NR^3SO_2CF_3$, NR^3SO_2 -phenyl,
 15 $S(O)_pCF_3$, $S(O)_p-C_{1-4}$ alkyl, $S(O)_p$ -phenyl, and $(CF_2)_rCF_3$;

R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl,
 phenyl substituted with 0-2 R^6 , and benzyl substituted
 with 0-2 R^6 ;

20

R^6 , at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$,
 halo, C_{1-4} alkyl, CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$,
 $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$,
 $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;

25

R^7 , at each occurrence, is selected from H, OH, C_{1-6} alkyl,
 C_{1-6} alkylcarbonyl, C_{1-6} alkoxy, C_{1-4} alkoxycarbonyl,
 $(CH_2)_n$ -phenyl, C_{6-10} aryloxy, C_{6-10} aryloxycarbonyl, C_{6-10}
 arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4}
 30 alkoxycarbonyl, C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl,
 C_{1-6} alkylaminocarbonyl, phenylaminocarbonyl, and phenyl
 C_{1-4} alkoxycarbonyl;

R^8 , at each occurrence, is selected from H, C_{1-6} alkyl and
 35 $(CH_2)_n$ -phenyl;

alternatively, R^7 and R^8 combine to form a 5 or 6 membered
 saturated, ring which contains from 0-1 additional

heteroatoms selected from the group consisting of N, O,
and S;

5 R^9 , at each occurrence, is selected from H, C_{1-6} alkyl and
(CH_2) $_n$ -phenyl;

n , at each occurrence, is selected from 0, 1, 2, and 3;

10 m , at each occurrence, is selected from 0, 1, and 2;

p , at each occurrence, is selected from 0, 1, and 2;

r , at each occurrence, is selected from 0, 1, 2, and 3;

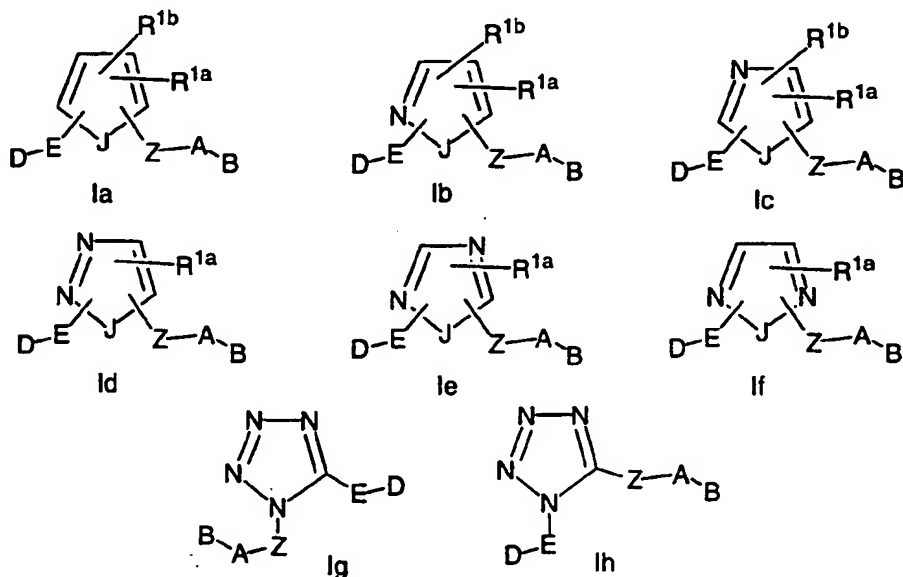
15 s , at each occurrence, is selected from 0, 1, and 2; and,

t , at each occurrence, is selected from 0, 1, 2, and 3;

20 provided that D-E-G-(CH_2) $_s$ - and -Z-A-B are not both
benzamidines.

[2] In a preferred embodiment, the present invention provides
novel compounds of formulae Ia-Ih:

25



wherein, groups D-E- and -Z-A-B are attached to adjacent atoms on the ring;

5 R is selected from H, Cl, F, Br, I, $(\text{CH}_2)_t\text{OR}^3$, C_{1-4} alkyl, OCF_3 , CF_3 , $\text{C}(\text{O})\text{NR}^7\text{R}^8$, and $(\text{CR}^8\text{R}^9)_t\text{NR}^7\text{R}^8$;

10 Z is selected from a CH_2O , OCH_2 , CH_2NH , NHCH_2 , $\text{C}(\text{O})$, $\text{CH}_2\text{C}(\text{O})$, $\text{C}(\text{O})\text{CH}_2$, $\text{NHC}(\text{O})$, $\text{C}(\text{O})\text{NH}$, $\text{CH}_2\text{S}(\text{O})_2$, $\text{S}(\text{O})_2(\text{CH}_2)$, SO_2NH , and NHSO_2 , provided that Z does not form a N-N, N-O, NCH_2N , or NCH_2O bond with ring M or group A;

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4 ;
 15 phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,
 20 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, 25 benzisothiazolyl, and isoindazolyl;

B is selected from: Y, X-Y, NR^2R^{2a} , $\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$, and $\text{NR}^2\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$;

30 X is selected from C_{1-4} alkylene, $-\text{C}(\text{O})-$, $-\text{C}(=\text{NR})-$, $-\text{CR}^2(\text{NR}^2\text{R}^{2a})-$, $-\text{C}(\text{O})\text{CR}^2\text{R}^{2a}-$, $-\text{CR}^2\text{R}^{2a}\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^2-$, $-\text{NR}^2\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^2\text{CR}^2\text{R}^{2a}-$, $-\text{NR}^2\text{C}(\text{O})\text{CR}^2\text{R}^{2a}-$, $-\text{CR}^2\text{R}^{2a}\text{C}(\text{O})\text{NR}^2-$, $-\text{CR}^2\text{R}^{2a}\text{NR}^2\text{C}(\text{O})-$, $-\text{NR}^2\text{C}(\text{O})\text{NR}^2-$, $-\text{NR}^2-$, $-\text{NR}^2\text{CR}^2\text{R}^{2a}-$, $-\text{CR}^2\text{R}^{2a}\text{NR}^2-$, O, $-\text{CR}^2\text{R}^{2a}\text{O}-$, and $-\text{OCR}^2\text{R}^{2a}-$;

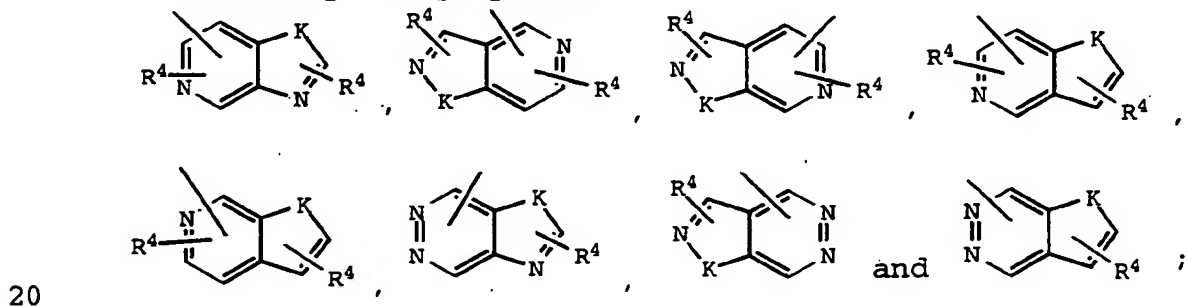
35

Y is NR^2R^{2a} , provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

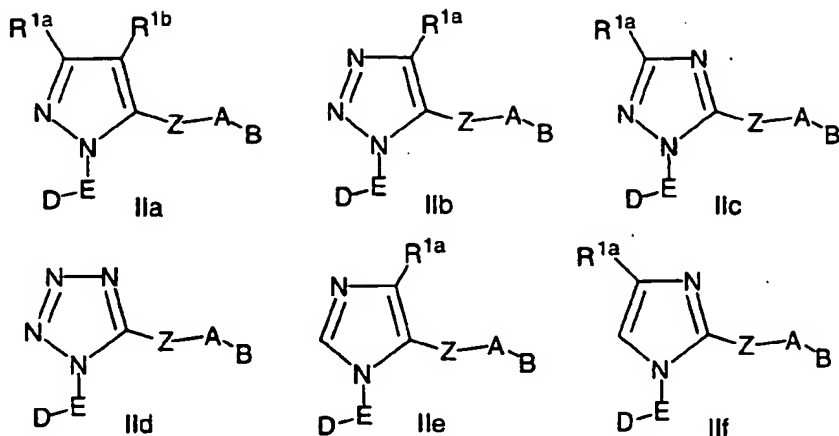
5 cylcopropyl, cyclopentyl, cyclohexyl, phenyl,
 piperidiny1, piperaziny1, pyridyl, pyrimidyl, furanyl,
 morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl,
 oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl,
 isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl,
 thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,
 10 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,
 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,
 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl,
 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl,
 benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl,
 15 benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl,
 benzisothiazolyl, and isoindazolyl;

alternatively, Y is selected from the following bicyclic heteroaryl ring systems:



K is selected from O, S, NH, and N.

25 [3] In a more preferred embodiment, the present invention provides novel compounds of formulae IIa-IIf:



wherein;

- 5 Z is selected from a C(O), CH₂C(O), C(O)CH₂, NHC(O), C(O)NH, C(O)N(CH₃), CH₂S(O)₂, S(O)₂(CH₂), SO₂NH, and NHSO₂, provided that Z does not form a N-N or NCH₂N bond with ring M or group A.

10

[4] In an even more preferred embodiment, the present invention provides novel compounds of formulae IIa-IIf, wherein;

- 15 E is phenyl substituted with R or 2-pyridyl substituted with R;

D is selected from NH₂, NHCH₃, CH₂NH₂, CH₂NHCH₃, CH(CH₃)NH₂, and C(CH₃)₂NH₂, provided that D is substituted ortho to ring M on E; and,

20

R is selected from H, OCH₃, Cl, and F.

- 25 [5] In a further preferred embodiment, the present invention provides novel compounds of formulae IIa-IIf, wherein;

D-E is selected from 2-aminophenyl, 2-methylaminophenyl, 2-aminomethylphenyl, 4-methoxy-2-aminophenyl, 4-methoxy-2-

(methylamino)phenyl, 4-methoxy-2-aminomethylphenyl, 4-methoxy-2-(methylaminomethyl)phenyl, 4-methoxy-2-(1-aminoethyl)phenyl, 4-methoxy-2-(2-amino-2-propyl)phenyl, 4-Cl-2-aminophenyl, 4-Cl-2-(methylamino)phenyl, 4-Cl-2-aminomethylphenyl, 4-Cl-2-(methylaminomethyl)phenyl, 4-Cl-2-(1-aminoethyl)phenyl, 4-Cl-2-(2-amino-2-propyl)phenyl, 4-F-2-aminophenyl, 4-F-2-(methylamino)phenyl, 4-F-2-aminomethylphenyl, 4-F-2-(methylaminomethyl)phenyl, 4-F-2-(1-aminoethyl)phenyl, and 4-F-2-(2-amino-2-propyl)phenyl.

[6] In another even more preferred embodiment, the present invention provides novel compounds of formulae IIa-IIf, wherein;

Z is $C(O)CH_2$ and $CONH$, provided that Z does not form a N-N bond with group A;

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R^4 ; and,

B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R^{4a} ;

R^4 , at each occurrence, is selected from OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, $(CH_2)_rNR^2R^{2a}$, and $(CF_2)_rCF_3$;

R^{4a} is selected from C_{1-4} alkyl, CF_3 , $S(O)_pR^5$, $SO_2NR^2R^{2a}$, and 1- CF_3 -tetrazol-2-yl;

R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl, phenyl, and benzyl;

X is CH_2 or $C(O)$; and,

Y is selected from pyrrolidino and morpholino.

[7] In another further preferred embodiment, the present invention provides novel compounds of formulae IIa-IIf, wherein;

A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

B is selected from the group: 2-CF₃-phenyl, 2-(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 2-(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 4-morpholino, 2-(1'-CF₃-tetrazol-2-yl)phenyl, 4-morpholinocarbonyl, 2-methyl-1-imidazolyl, 5-methyl-1-imidazolyl, 2-methylsulfonyl-1-imidazolyl and, 5-methyl-1,2,3-triazolyl.

20

[8] In another even more preferred embodiment, the present invention provides novel compounds of formulae IIa-IIf, wherein;

E is phenyl substituted with R or 2-pyridyl substituted with R;

D is selected from NH₂, NHCH₃, CH₂NH₂, CH₂NHCH₃, CH(CH₃)NH₂, and C(CH₃)₂NH₂, provided that D is substituted ortho to ring M on E; and,

R is selected from H, OCH₃, Cl, and F;

Z is C(O)CH₂ and CONH, provided that Z does not form a N-N bond with group A;

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R⁴; and,

- B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R^{4a};
- 5 R⁴, at each occurrence, is selected from OH, (CH₂)_rOR², halo, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, and (CF₂)_rCF₃;
- 10 R^{4a} is selected from C₁₋₄ alkyl, CF₃, S(O)_pR⁵, SO₂NR²R^{2a}, and 1-CF₃-tetrazol-2-yl;
- R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;
- 15 X is CH₂ or C(O); and,
- Y is selected from pyrrolidino and morpholino.
- 20 [9] In another further preferred embodiment, the present invention provides novel compounds of formulae IIa-IIf, wherein;
- 25 D-E is selected from 2-aminophenyl, 2-methylaminophenyl, 2-aminomethylphenyl, 4-methoxy-2-aminophenyl, 4-methoxy-2-(methylamino)phenyl, 4-methoxy-2-aminomethylphenyl, 4-methoxy-2-(methylaminomethyl)phenyl, 4-methoxy-2-(1-aminoethyl)phenyl, 4-methoxy-2-(2-amino-2-propyl)phenyl, 4-Cl-2-aminophenyl, 4-Cl-2-(methylamino)phenyl, 4-Cl-2-aminomethylphenyl, 4-Cl-2-(methylaminomethyl)phenyl, 4-Cl-2-(1-aminoethyl)phenyl, 4-Cl-2-(2-amino-2-propyl)phenyl, 4-F-2-aminophenyl, 4-F-2-(methylamino)phenyl, 4-F-2-aminomethylphenyl, 4-F-2-(methylaminomethyl)phenyl, 4-F-2-(1-aminoethyl)phenyl, 30 and 4-F-2-(2-amino-2-propyl)phenyl;
- 35 A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-

phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

B is selected from the group: 2-CF₃-phenyl, 2-
5 (aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 2-(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 4-morpholino, 2-(1'-CF₃-tetrazol-2-yl)phenyl, 4-morpholinocarbonyl, 2-methyl-1-imidazolyl, 5-methyl-1-imidazolyl, 2-methylsulfonyl-1-imidazolyl and,
10 5-methyl-1,2,3-triazolyl.

[10] In a still further preferred embodiment, the present invention provides a novel compound of formula IIa.
15

[11] In another still further preferred embodiment, the present invention provides a novel compound of formula IIb.

20 [12] In another still further preferred embodiment, the present invention provides a novel compound of formula IIc.

25 [13] In another still further preferred embodiment, the present invention provides a novel compound of formula IIId.

[14] In another still further preferred embodiment, the present invention provides a novel compound of formula IIe.
30

[15] In another still further preferred embodiment, the present invention provides a novel compound of formula IIIf.
35

[16] In another even more preferred embodiment, the present invention provides novel compounds of formulae IIa-IIf, wherein;

5 D is selected from $-\text{CN}$, $\text{C}(=\text{NR}^8)\text{NR}^7\text{R}^9$, $\text{C}(\text{O})\text{NR}^7\text{R}^8$, NR^7R^8 , and $\text{CH}_2\text{NR}^7\text{R}^8$, provided that D is substituted ortho to ring M on E;

E is phenyl substituted with R or pyridyl substituted with R;

10

R is selected from H, Cl, F, OR^3 , CH_3 , CH_2CH_3 , OCF_3 , CF_3 , NR^7R^8 , and $\text{CH}_2\text{NR}^7\text{R}^8$;

15

Z is selected from $\text{C}(\text{O})$, $\text{CH}_2\text{C}(\text{O})$, $\text{C}(\text{O})\text{CH}_2$, $\text{NHC}(\text{O})$, and $\text{C}(\text{O})\text{NH}$, provided that Z does not form a N-N bond with ring M or group A;

R^{1a} and R^{1b} are independently absent or selected from
20 $-(\text{CH}_2)_r-\text{R}^{1'}$, $\text{NCH}_2\text{R}^{1'}$, $\text{OCH}_2\text{R}^{1'}$, $\text{SCH}_2\text{R}^{1'}$, $\text{N}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$, $\text{O}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$, and $\text{S}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$, or combined to form a 5-8 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^4 and which contains from 0-2 heteroatoms selected from the group consisting of N, O, and S;

25

$\text{R}^{1'}$, at each occurrence, is selected from H, C_{1-3} alkyl, halo, $(\text{CF}_2)_r\text{CF}_3$, OR^2 , NR^2R^{2a} , $\text{C}(\text{O})\text{R}^{2c}$, $(\text{CF}_2)_r\text{CO}_2\text{R}^{2c}$, $\text{S}(\text{O})_p\text{R}^{2b}$, $\text{NR}^2(\text{CH}_2)_r\text{OR}^2$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{NR}^2\text{C}(\text{O})_2\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$, and $\text{NR}^2\text{SO}_2\text{R}^{2b}$;

30

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4 ;
phenyl, piperidinyl, piperazinyl, pyridyl,
pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,
35 pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, and imidazolyl;

B is selected from: Y, X-Y, NR^2R^{2a} , $\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$, and $\text{NR}^2\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$;

5 X is selected from CH_2 , $-\text{CR}^2(\text{CR}^2\text{R}^{2b})(\text{CH}_2)_t-$, $-\text{C}(\text{O})-$, $-\text{C}(=\text{NR})-$, $-\text{CH}(\text{NR}^2\text{R}^{2a})-$, $-\text{C}(\text{O})\text{NR}^2-$, $-\text{NR}^2\text{C}(\text{O})-$, $-\text{NR}^2\text{C}(\text{O})\text{NR}^2-$, $-\text{NR}^2-$, and O;

Y is NR^2R^{2a} , provided that X-Y do not form a N-N or O-N bond;

10 alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a} ;

phenyl, piperidinyl, piperazinyl, pyridyl,
pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,
15 pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl,
thiazolyl, isothiazolyl, pyrazolyl, imidazolyl,
oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,
1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,
1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,
20 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl,
1,2,4-triazolyl, 1,2,5-triazolyl, and 1,3,4-triazolyl;

R^4 , at each occurrence, is selected from =O, OH, Cl, F, C_{1-4} alkyl, $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$, $(\text{CH}_2)_r\text{C}(\text{O})\text{R}^{2b}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$,
25 $\text{CH}(=\text{NH})\text{NH}_2$, $\text{NHC}(=\text{NH})\text{NH}_2$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2-\text{C}_{1-4}$ alkyl, $\text{NR}^2\text{SO}_2\text{R}^5$, $\text{S}(\text{O})_p\text{R}^5$, and $(\text{CF}_2)_r\text{CF}_3$;

R^{4a} , at each occurrence, is selected from =O, OH, Cl, F, C_{1-4} alkyl, $(\text{CH}_2)_r\text{NR}^2\text{R}^{2a}$, $(\text{CH}_2)_r\text{C}(\text{O})\text{R}^{2b}$, $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$,
30 $\text{CH}(=\text{NH})\text{NH}_2$, $\text{NHC}(=\text{NH})\text{NH}_2$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2-\text{C}_{1-4}$ alkyl, $\text{NR}^2\text{SO}_2\text{R}^5$, $\text{S}(\text{O})_p\text{R}^5$, $(\text{CF}_2)_r\text{CF}_3$, and 1- CF_3 -tetrazol-2-yl;

R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl, phenyl substituted with 0-2 R^6 , and benzyl substituted
35 with 0-2 R^6 ;

R⁶, at each occurrence, is selected from H, =O, OH, OR², Cl, F, CH₃, CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2b}, NR²C(O)R^{2b}, CH(=NH)NH₂, NHC(=NH)NH₂, and SO₂NR²R^{2a};

5 R⁷, at each occurrence, is selected from H, OH, C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₄ alkoxy carbonyl, benzyl, C₆₋₁₀ aryloxy, C₆₋₁₀ aryloxy carbonyl, C₆₋₁₀ arylmethylcarbonyl, C₁₋₄ alkylcarbonyloxy C₁₋₄ alkoxy carbonyl, C₆₋₁₀ arylcarbonyloxy C₁₋₄ alkoxy carbonyl,
10 C₁₋₆ alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C₁₋₄ alkoxy carbonyl;

R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and benzyl; and

15 alternatively, R⁷ and R⁸ combine to form a morpholino group; and,

R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and
20 benzyl.

[17] In a another further preferred embodiment, the present invention provides novel compounds of formulae IIa-IIf,
25 wherein;

E is phenyl substituted with R or 2-pyridyl substituted with R;

30 R is selected from H, Cl, F, OCH₃, CH₃, OCF₃, CF₃, NH₂, and CH₂NH₂;

Z is selected from a C(O)CH₂ and C(O)NH, provided that Z does not form a N-N bond with group A;

35 R^{1a} is selected from H, CH₃, CH₂CH₃, Cl, F, CF₃, OCH₃, NR²R^{2a}, S(O)_pR^{2b}, CH₂S(O)_pR^{2b}, CH₂NR²S(O)_pR^{2b}, C(O)R^{2c}, CH₂C(O)R^{2c}, C(O)NR²R^{2a}, and SO₂NR²R^{2a};

R^{1b} is selected from H, CH_3 , CH_2CH_3 , Cl, F, CF_3 , OCH_3 , NR^2R^{2a} , $S(O)_pR^{2b}$, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, $C(O)NR^2R^{2a}$, and $SO_2NR^2R^{2a}$;

5

A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4 ; phenyl, pyridyl, pyrimidyl, furanyl, thiophenyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, and imidazolyl;

10

B is selected from: Y and X-Y;

X is selected from CH_2 , $-CR^2(CR^2R^{2b})-$, $-C(O)-$, $-C(=NR)-$, $-CH(NR^2R^{2a})-$, $-C(O)NR^2-$, $-NR^2C(O)-$, $-NR^2C(O)NR^2-$, $-NR^2-$, and O;

15

Y is NR^2R^{2a} , provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a} ;

20

phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, and 1,3,4-triazolyl;

25

30

R^2 , at each occurrence, is selected from H, CF_3 , CH_3 , benzyl, and phenyl;

35

R^{2a} , at each occurrence, is selected from H, CF_3 , CH_3 , benzyl, and phenyl;

R^{2b}, at each occurrence, is selected from CF₃, OCH₃, CH₃,
benzyl, and phenyl;

5 R^{2c}, at each occurrence, is selected from CF₃, OH, OCH₃, CH₃,
benzyl, and phenyl;

alternatively, R² and R^{2a} combine to form a 5 or 6 membered
saturated, partially unsaturated, or unsaturated ring
which contains from 0-1 additional heteroatoms selected
10 from the group consisting of N, O, and S;

R³, at each occurrence, is selected from H, CH₃, CH₂CH₃, and
phenyl;

15 R^{3a}, at each occurrence, is selected from H, CH₃, CH₂CH₃, and
phenyl;

R⁴, at each occurrence, is selected from OH, Cl, F, CH₃,
CH₂CH₃, NR²R^{2a}, CH₂NR²R^{2a}, C(O)R^{2b}, NR²C(O)R^{2b}, C(O)NR²R^{2a},
20 and CF₃;

R^{4a}, at each occurrence, is selected from OH, Cl, F, CH₃,
CH₂CH₃, NR²R^{2a}, CH₂NR²R^{2a}, C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a},
S(O)_pR⁵, CF₃, and 1-CF₃-tetrazol-2-yl;

25 R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl,
phenyl substituted with 0-2 R⁶, and benzyl substituted
with 1 R⁶;

30 R⁶, at each occurrence, is selected from H, OH, OCH₃, Cl, F,
CH₃, CN, NO₂, NR²R^{2a}, CH₂NR²R^{2a}, and SO₂NR²R^{2a};

R⁷, at each occurrence, is selected from H and C₁₋₃ alkyl;

35 R⁸, at each occurrence, is selected from H, CH₃, and benzyl;

R⁹, at each occurrence, is selected from H, CH₃, and benzyl;
and,

t, at each occurrence, is selected from 0 and 1:

- 5 [18] In a another still further preferred embodiment, the present invention provides novel compounds of formulae IIa-IIf, wherein;

10 D is selected from NR^7R^8 , and $\text{CH}_2\text{NR}^7\text{R}^8$, provided that D is substituted ortho to ring M on E;

R^{1a} is absent or is selected from H, CH_3 , CH_2CH_3 , Cl, F, CF_3 , OCH_3 , NR^2R^{2a} , $\text{S}(\text{O})_p\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{CH}_2\text{S}(\text{O})_p\text{R}^{2b}$, $\text{CH}_2\text{NR}^2\text{S}(\text{O})_p\text{R}^{2b}$, $\text{C}(\text{O})\text{R}^{2c}$, $\text{CH}_2\text{C}(\text{O})\text{R}^{2c}$, and $\text{SO}_2\text{NR}^2\text{R}^{2a}$;

15 R^{1b} is absent or is selected from H, CH_3 , CH_2CH_3 , Cl, F, CF_3 , OCH_3 , NR^2R^{2a} , $\text{S}(\text{O})_p\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{CH}_2\text{S}(\text{O})_p\text{R}^{2b}$, $\text{CH}_2\text{NR}^2\text{S}(\text{O})_p\text{R}^{2b}$, $\text{C}(\text{O})\text{R}^{2b}$, $\text{CH}_2\text{C}(\text{O})\text{R}^{2b}$, and $\text{SO}_2\text{NR}^2\text{R}^{2a}$;

20 A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^4 ; phenyl, pyridyl, and pyrimidyl;

B is selected from: Y and X-Y;

25 X is selected from $-\text{C}(\text{O})-$ and O;

Y is NR^2R^{2a} , provided that X-Y do not form a O-N bond;

30 alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a} ;

35 phenyl, piperazinyl, pyridyl, pyrimidyl, morpholinyl, pyrrolidinyl, imidazolyl, and 1,2,3-triazolyl;

R^2 , at each occurrence, is selected from H, CF_3 , CH_3 , benzyl, and phenyl;

- R^{2a} , at each occurrence, is selected from H, CF_3 , CH_3 , benzyl, and phenyl;
- 5 R^{2b} , at each occurrence, is selected from CF_3 , OCH_3 , CH_3 , benzyl, and phenyl;
- R^{2c} , at each occurrence, is selected from CF_3 , OH, OCH_3 , CH_3 , benzyl, and phenyl;
- 10 alternatively, R^2 and R^{2a} combine to form a ring system selected from pyrrolidinyl, piperazinyl and morpholino;
- R^4 , at each occurrence, is selected from Cl, F, CH_3 , NR^2R^{2a} , and CF_3 ;
- 15 R^{4a} , at each occurrence, is selected from Cl, F, CH_3 , $SO_2NR^2R^{2a}$, $S(O)_pR^5$, and CF_3 ;
- 20 R^5 , at each occurrence, is selected from CF_3 and CH_3 ;
- R^7 , at each occurrence, is selected from H, CH_3 , and CH_2CH_3 ; and,
- 25 R^8 , at each occurrence, is selected from H and CH_3 .
- [19] Specifically preferred compounds of the present invention are selected from the group:
- 30 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 35 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 40 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;

- 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 5 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 10
- 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 15 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 20
- 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 25
- 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 30
- 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 35
- 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 40
- 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 45
- 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 50
- 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;

- 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 5 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 10 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 15 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 20 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 25 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 30 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(1-pyrrolidinocarbonyl)phenyl))carboxamide;
- 35 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(1-pyrrolidinocarbonyl)phenyl))carboxamide;
- 40 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(1-pyrrolidinocarbonyl)phenyl))carboxamide;
- 45 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(1-pyrrolidinocarbonyl)phenyl))carboxamide;
- 50 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(1-pyrrolidinocarbonyl)phenyl))carboxamide;
- 55 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(1-pyrrolidinocarbonyl)phenyl))carboxamide;

- 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-(1-pyrrolidinocarbonyl)phenyl)carboxamide;
- 5 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-(1-pyrrolidinocarbonyl)carboxamide;
- 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-(1-pyrrolidinocarbonyl)phenyl)carboxamide;
- 10 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyridin-2-yl)carboxamide;
- 15 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyridin-2-yl)carboxamide;
- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyridin-2-yl)carboxamide;
- 20 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyridin-2-yl)carboxamide;
- 25 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyridin-2-yl)carboxamide;
- 30 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyridin-2-yl)carboxamide;
- 35 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyridin-2-yl)carboxamide;
- 40 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyridin-2-yl)carboxamide;
- 45 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyridin-2-yl)carboxamide;
- 50 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyridin-2-yl)carboxamide;
- 55 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyridin-2-yl)carboxamide;
- 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyridin-2-yl)carboxamide;
- 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyrimidin-2-yl)carboxamide;

- 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyrimidin-2-yl)carboxamide;
- 5 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyrimidin-2-yl)carboxamide;
- 10 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyrimidin-2-yl)carboxamide;
- 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyrimidin-2-yl)carboxamide;
- 15 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyrimidin-2-yl)carboxamide;
- 20 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyrimidin-2-yl)carboxamide;
- 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyrimidin-2-yl)carboxamide;
- 25 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyrimidin-2-yl)carboxamide;
- 30 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyrimidin-2-yl)carboxamide;
- 35 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyrimidin-2-yl)carboxamide;
- 40 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyrimidin-2-yl)carboxamide;
- 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 45 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 50 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 55

- 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 5 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 10 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 15 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 20 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 25 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 30 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 35 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 40 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 45 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 50 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 55 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;

- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 5 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 10 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((5-methyl)imidazo-1-yl)phenyl)carboxamide; and,
- 15 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;

and pharmaceutically acceptable salts thereof.

- 20 [20] More specifically preferred compounds of the present invention are selected from the group:

- 25 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 5-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-3-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 30 3-Methyl-1-(2-N,N-dimethylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-N-methylsulfamido-[1,1']-biphen-4-yl))carboxamide;
- 35 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1]-biphen-4-yl))carboxamide;
- 40 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide;
- 45 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide;
- 50 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1]-biphen-4-yl))carboxamide;
- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-pyrrolidinocarbonyl)phenyl)carboxamide;

- N-Benzylsulfonyl-4-(3-trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxyamido)piperidine;
- 5 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2'-sulfonamido)phenyl)pyrid-2-yl)carboxyamide;
- 10 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(pyrid-2-yl))pyrid-2-yl)carboxyamide;
- N-Benzyl-4-(3-trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxyamido)piperidine;
- 15 N-Phenylsulfonyl-4-(3-trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxyamido)piperidine;
- 20 3-Trifluoromethyl-1-(2-aminomethyl-4-chlorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxyamide;
- 3-Trifluoromethyl-1-(2-aminomethyl-4-chlorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxyamide;
- 25 3-Trifluoromethyl-1-(2-aminomethyl-5-chlorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxyamide;
- 30 3-Trifluoromethyl-1-(2-aminomethyl-4-chlorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxyamide;
- 35 3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxyamide;
- 40 3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxyamide;
- 45 3-Trifluoromethyl-1-(2-aminomethyl-5-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxyamide;
- 50 3-Trifluoromethyl-1-(2-aminomethyl-4,5-difluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxyamide;
- 55 3-Trifluoromethyl-1-(2-aminomethyl-4,5-difluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxyamide;

- 3-Trifluoromethyl-1-(2-aminomethyl-3-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 5 3-Trifluoromethyl-1-(2-aminomethyl-3-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 10 3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(4-(2-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 15 3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(4-(2-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 20 3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(4-(N-(N-methylsulfonyl)iminolyl)pyrrolidino))phenyl)carboxamide;
- 25 3-Trifluoromethyl-1-(2-(N-glycyl)aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 30 3-Trifluoromethyl-1-(2-(N-phenylacetyl)aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 35 3-(Trifluoromethyl)-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 40 3-Trifluoromethyl-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 45 3-Trifluoromethyl-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 50 3-Trifluoromethyl-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 55 3-Trifluoromethyl-1-(2-(N-(N-methylglycyl)aminomethyl)phenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;

- 3-Trifluoromethyl-1-(2-cyanophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 5 1-(2'-Aminomethylphenyl)-5-[(2'-methylsulfonyl)-3-fluoro-[1,1']-biphen-4-yl]aminocarbonyl]-tetrazole;
- 1-(2'-Aminomethylphenyl)-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]-tetrazole;
- 10 1-[2-(Aminomethyl)phenyl]-3-thiomethoxy-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;
- 15 1-[2-(Aminomethyl)phenyl]-3-methylsulfonyl-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;
- 1-[2-(Aminomethyl)phenyl]-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]triazole;
- 20 1-[2-(Aminomethyl)phenyl]-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;
- 1-[2-(Aminomethyl)phenyl]-3-trifluoromethyl-5-[(2-fluoro)-(2'-pyrrolidinomethyl)-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole; and,
- 25 1-[2-(Aminomethyl)phenyl]-3-trifluoromethyl-5-[(2-fluoro)-(2'-hydroxymethyl)-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;
- 30 and pharmaceutically acceptable salts thereof.

In a second embodiment, the present invention provides
35 novel pharmaceutical compositions, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

40 In a third embodiment, the present invention provides a novel method for treating or preventing a thromboembolic disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form
45 thereof.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically
5 active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double
10 bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all
15 geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated. All processes used to prepare compounds of the present invention and intermediates made therein are considered to be part of the present invention.

20 The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent
25 is keto (i.e., =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties.

The present invention is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass
30 numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium. Isotopes of carbon include C-13 and C-14.

When any variable (e.g., R⁶) occurs more than one time in any constituent or formula for a compound, its definition at
35 each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R⁶, then said group may optionally be substituted with up to two R⁶ groups and R⁶ at each occurrence

is selected independently from the definition of R^6 . Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond
5 connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such
10 substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon
15 groups having the specified number of carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups
20 having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where $v = 1$ to 3 and $w = 1$ to $(2v+1)$). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents
25 an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated
30 ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. "Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl. "Alkynyl" is
35 intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon bonds which may occur in any stable point along the chain, such as ethynyl and propynyl.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, and sulfate.

5 As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7-to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to,
10 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane, [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, and tetrahydronaphthyl.

15 As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and
20 from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached
25 to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. A nitrogen in the heterocycle may optionally be quaternized. It is preferred
30 that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" or "heteroaryl" is
35 intended to mean a stable 5-to 7-membered monocyclic or bicyclic or 7-to 10-membered bicyclic heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting of N, O and

S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl,

- 5 benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl,
- 10 dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolenyl, indolinyl, indoliziny, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl,
- 15 morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl,
- 20 phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl,
- 25 4H-quinoliziny, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl,
- 30 thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl,
- 35 benzimidazolyl, 1H-indazolyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues
5 of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer
10 to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic
15 residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts
20 include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic,
25 hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present
30 invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water
35 or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical*

Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

"Prodrugs" are intended to include any covalently bonded carriers which release the active parent drug according to formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of formula (I) are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of formula (I) wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug or compound of formula (I) is administered to a mammalian subject, cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of formula (I), and the like. Preferred prodrugs are amidine prodrugs wherein D is $C(=NR^7)NH_2$ or its tautomer $C(=NH)NHR^7$ and R^7 is selected from OH, C_{1-4} alkoxy, C_{6-10} aryloxy, C_{1-4} alkoxycarbonyl, C_{6-10} aryloxycarbonyl, C_{6-10} arylmethylcarbonyl, C_{1-4} alkylcarbonyloxy C_{1-4} alkoxycarbonyl, and C_{6-10} arylcarbonyloxy C_{1-4} alkoxycarbonyl. More preferred prodrugs are where R^7 is OH, methoxy, ethoxy, benzyloxycarbonyl, methoxycarbonyl, and methylcarbonyloxymethoxycarbonyl.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Substituted" is intended to indicate that one or more hydrogens on the atom indicated in the expression using "substituted" is replaced with a selection from the indicated group(s), provided that the indicated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O) group, then 2 hydrogens on the atom are replaced.

"Therapeutically effective amount" is intended to include an amount of a compound of the present invention or an amount of the combination of compounds claimed effective to inhibit HIV infection or treat the symptoms of HIV infection in a host. The combination of compounds is preferably a synergistic combination. Synergy, as described for example by Chou and Talalay, Adv. Enzyme Regul. 22:27-55 (1984), occurs when the effect (in this case, inhibition of HIV replication) of the compounds when administered in combination is greater than the additive effect of the compounds when administered alone as a single agent. In general, a synergistic effect is most clearly demonstrated at suboptimal concentrations of the compounds. Synergy can be in terms of lower cytotoxicity, increased antiviral effect, or some other beneficial effect of the combination compared with the individual components.

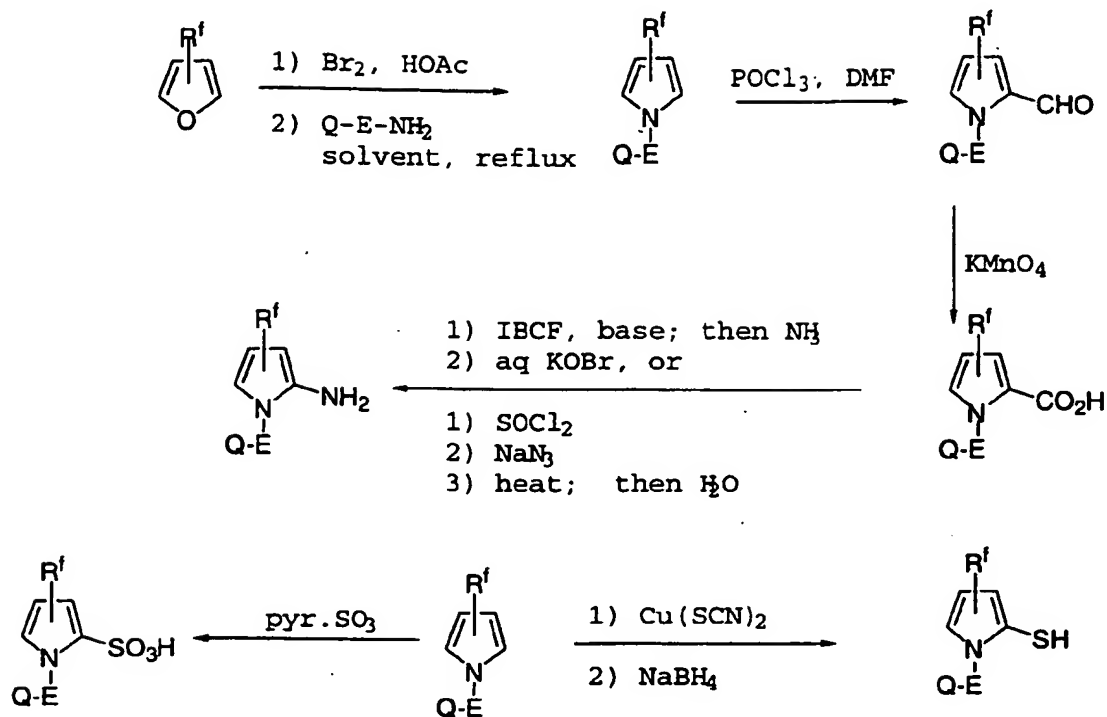
SYNTHESIS

The compounds of the present invention can be prepared in a number of ways known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or by variations thereon as appreciated by those skilled in the art. Preferred methods include, but are not limited to, those described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being effected. It will be understood by those skilled in the art of organic synthesis that the functionality present on the molecule should be consistent with the transformations proposed. This will sometimes require a judgment to modify the order of the synthetic steps or to select one particular process scheme over another in order to obtain a desired compound of the invention. It will also be recognized that another major consideration in the planning of any synthetic route in this field is the judicious choice of the protecting group used for protection of the reactive functional groups present in the compounds described in this invention. An

authoritative account describing the many alternatives to the trained practitioner is Greene and Wuts (*Protective Groups In Organic Synthesis*, Wiley and Sons, 1991). All references cited herein are hereby incorporated in their entirety herein by reference.

The compounds of Formula I in which ring M is pyrrole can be prepared by the procedures described in Schemes 1-9. In Scheme 1 is shown how to prepare pyrroles in which the group Q-E is attached to the pyrrole nitrogen, wherein Q is a functionality that can be converted into D of Formula I, R^e is functionality that can be converted into Z-A-B of Formula I and R^f is or can be converted into R^{1a} of Formula I. Oxidation of a furan with bromine in acetic acid can afford a 2,5-diacetoxidyhydrofuran which can react with amine Q-E-NH₂ to afford a pyrrole. Vilsmeier-Haack formylation with phosphorous oxychloride and DMF preferentially can acylate the pyrrole ring at C-2. Oxidation of the resulting aldehyde can give a carboxylic acid. The carboxylic acid can then be converted into amine derivatives using either the Hofmann degradation of the derived primary amide (Huisgen et. al. *Chem. Ber.* 1960, 93, 65) or the Curtius rearrangement of the derived acyl azide (*J. Prakt. Chem.* 1909, 42, 477). Derivatives which contain a sulfur atom attached to the pyrrole ring can be obtained by direct sulfonation with pyridine sulfur trioxide complex to give the sulfonic acids or treatment with copper (II) thiocyanate (*J. Het. Chem.* 1988, 25, 431) followed by the reduction of the intermediate thiocyanate with sodium borohydride to give a mercaptan.

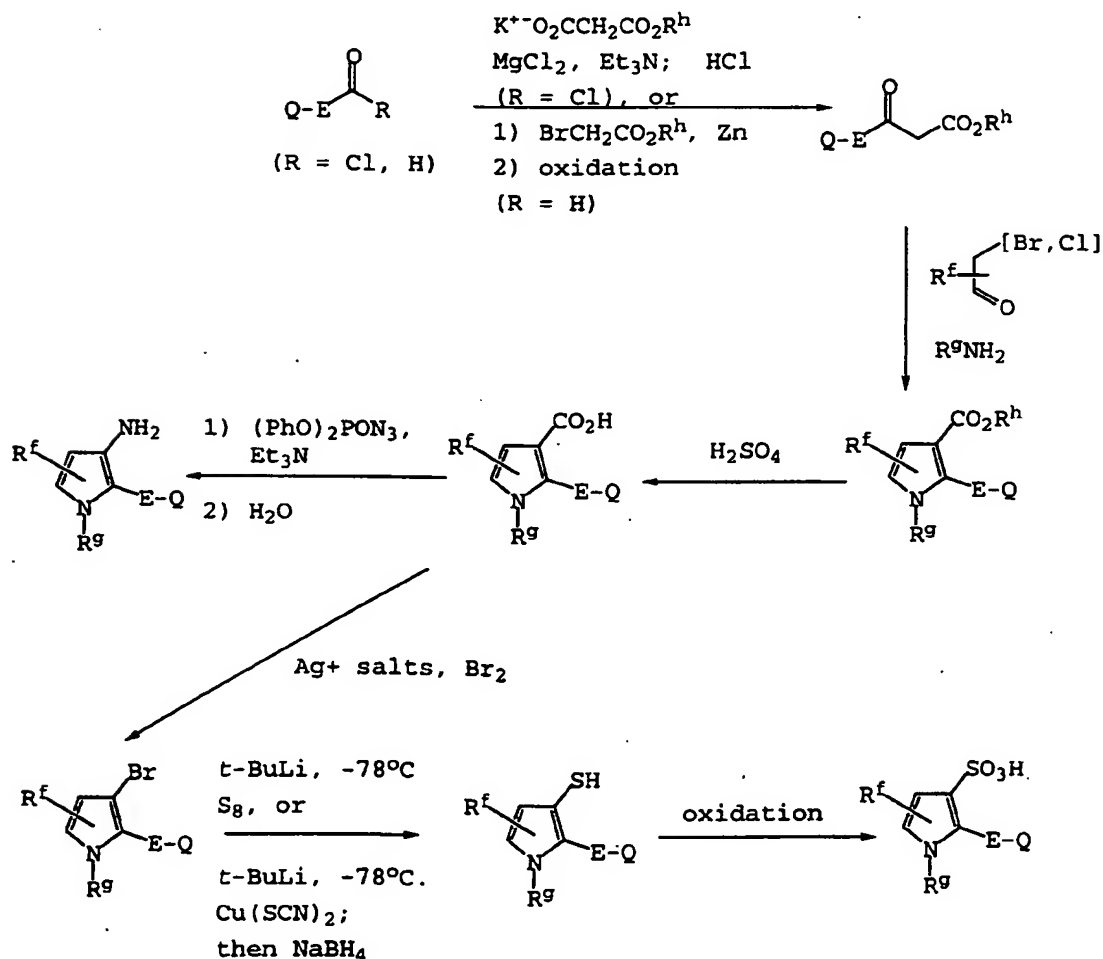
Scheme 1



- 5 In Scheme 2 is shown how to prepare pyrroles in which Q-E is attached to the 2-position, wherein R^f and R^g collectively are hydrogen or a group that can be converted into R^{1a} and R^{1b} of Formula I. The Hantzsch pyrrole synthesis is a versatile reaction involving the cyclization of an appropriate β -
- 10 ketoester with an α -halo ketone or aldehyde in the presence of a primary amine (*Ber. Dtsch. Chem. Ges.* **1890**, 23, 1474). The β -ketoesters can be prepared from acid chlorides ($\text{X} = \text{Cl}$) by the addition of the magnesium anion of potassium alkylmalonate followed by decarboxylation (*Synthesis* **1993**, 290).
- 15 Alternatively, β -ketoesters can be prepared from an appropriate aldehyde ($\text{R} = \text{H}$) by Reformatsky reaction with an α -bromoacetate followed by oxidation. Cyclization with an α -halo ketone or aldehyde in the presence of a primary amine can afford pyrroles. Acidic hydrolysis of the 3-carboalkoxy
- 20 pyrrole can afford the carboxylic acids. Pyrroles which contain a 3-amino substituent can be prepared from the acids by treatment with phosphoryl azide and triethylamine to effect a Curtius rearrangement to afford the isocyanates (*J. Med.*

Chem. 1981, 24, 33) which upon hydrolysis can yield 3-aminopyrroles. Pyrroles which contain a sulfur atom at C-3 can be prepared from the acids by employing the Hunsdiecker procedure to give the 3-bromo derivatives. Halogen-metal exchange at low temperature with an alkyl lithium reagent can afford the 3-lithio derivative which can be quenched with a variety of electrophiles, such as S_8 to afford thiols directly or $Cu(SCN)_2$ to afford a thiocyanate which can be reduced with sodium borohydride. The thiols can further be oxidized to the sulfonic acid derivatives by an oxidant such as $KMnO_4$.

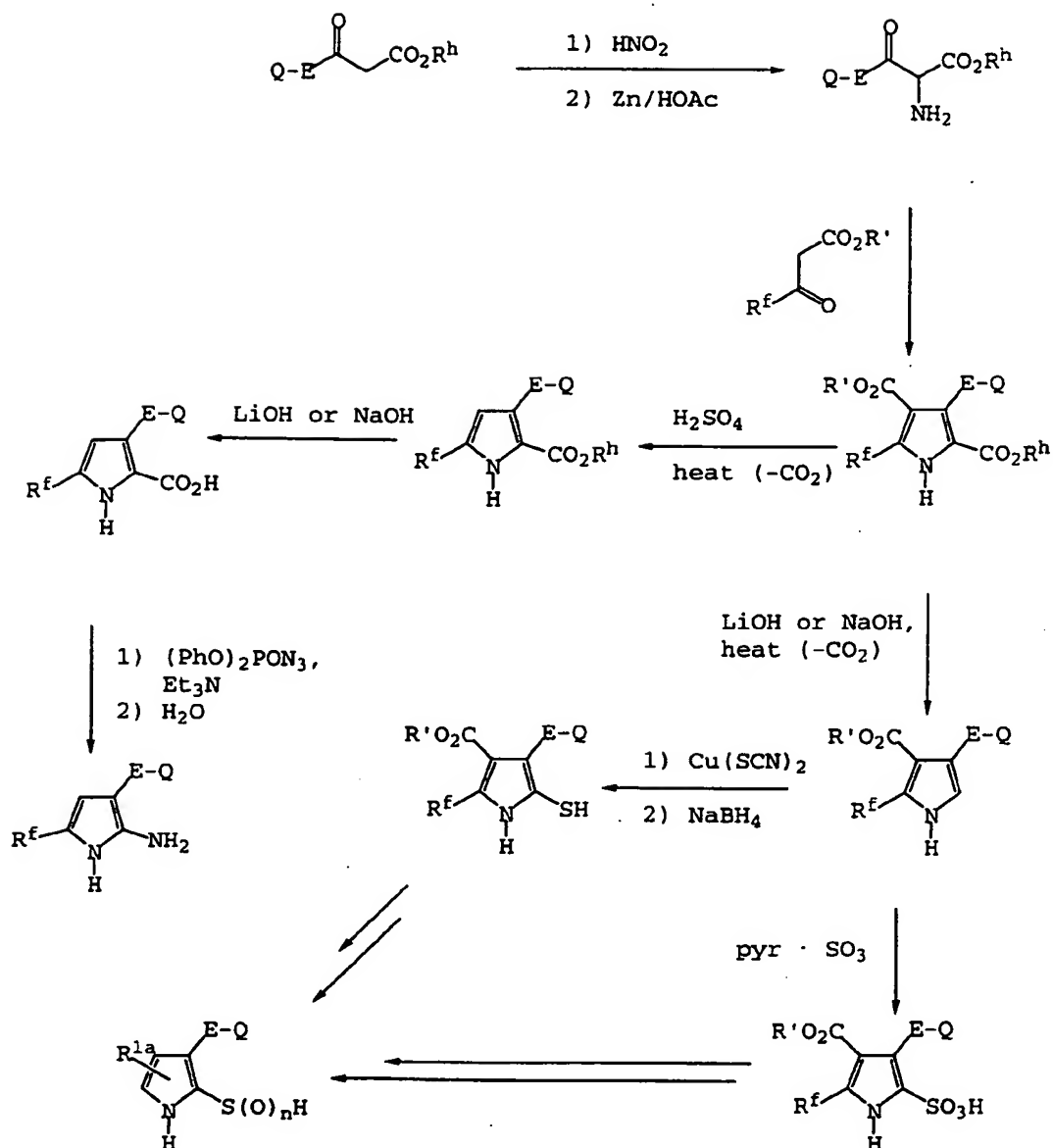
Scheme 2



15 In Scheme 3 is shown how to prepare pyrroles in which Q-E is attached to the 3-position. This scheme relies upon the extremely versatile Knorr pyrrole synthesis, which involves

- condensation of α -aminoketones with β -ketoesters. The α -aminoketones can be prepared from β -ketoesters (Scheme 2) by nitrosation followed by reduction with zinc/acetic acid. Condensation of α -aminoketones with appropriate β -ketoesters
- 5 can afford good yields of pyrroles. These intermediates are very versatile and can be converted into pyrroles with a wide variety of substituents with varying substitution patterns. For cases wherein R^e (Z-A-B precursor) is at the 2-position, acidic hydrolysis can selectively hydrolyze the C-3 ester.
- 10 Heating should then effect decarboxylation. Hydrolysis of the 2-carboxylic acid can be achieved under basic conditions. Curtius rearrangement of the acid as described previously can afford the amino derivatives. To prepare compounds with a sulfur atom attached to C-2, basic hydrolysis and
- 15 decarboxylation can afford the C-2 unsubstituted pyrroles. These pyrroles can undergo electrophilic substitution to afford thiols ($\text{Cu}(\text{SCN})_2$, then NaBH_4) and sulfonic acids (pyridine SO_3 complex or chlorosulfonic acid). The R^{1a} group contained in Formula I can be derived either from the
- 20 remaining ester or from R^f . Alternatively, the thiol and sulfonic acid derivatives can also be derived from the C-2 acids by manipulation of the carboxylic acid group as described previously.

Scheme 3



5 In Scheme 4 is shown how to prepare pyrroles in which Q-E
is attached to the 3-position. Cyclization of α -aminoketones
as described previously with β -ketoesters can afford pyrroles.
Hydrolysis under basic conditions can selectively hydrolyze
the C-2 ester which upon heating should undergo
10 decarboxylation to afford 2-unsubstituted pyrroles. The C-3
ester can then be hydrolyzed under acidic conditions to afford
the 3-carboxypyrroles. Curtius rearrangement under conditions
described previously can afford the 3-aminopyrroles. The

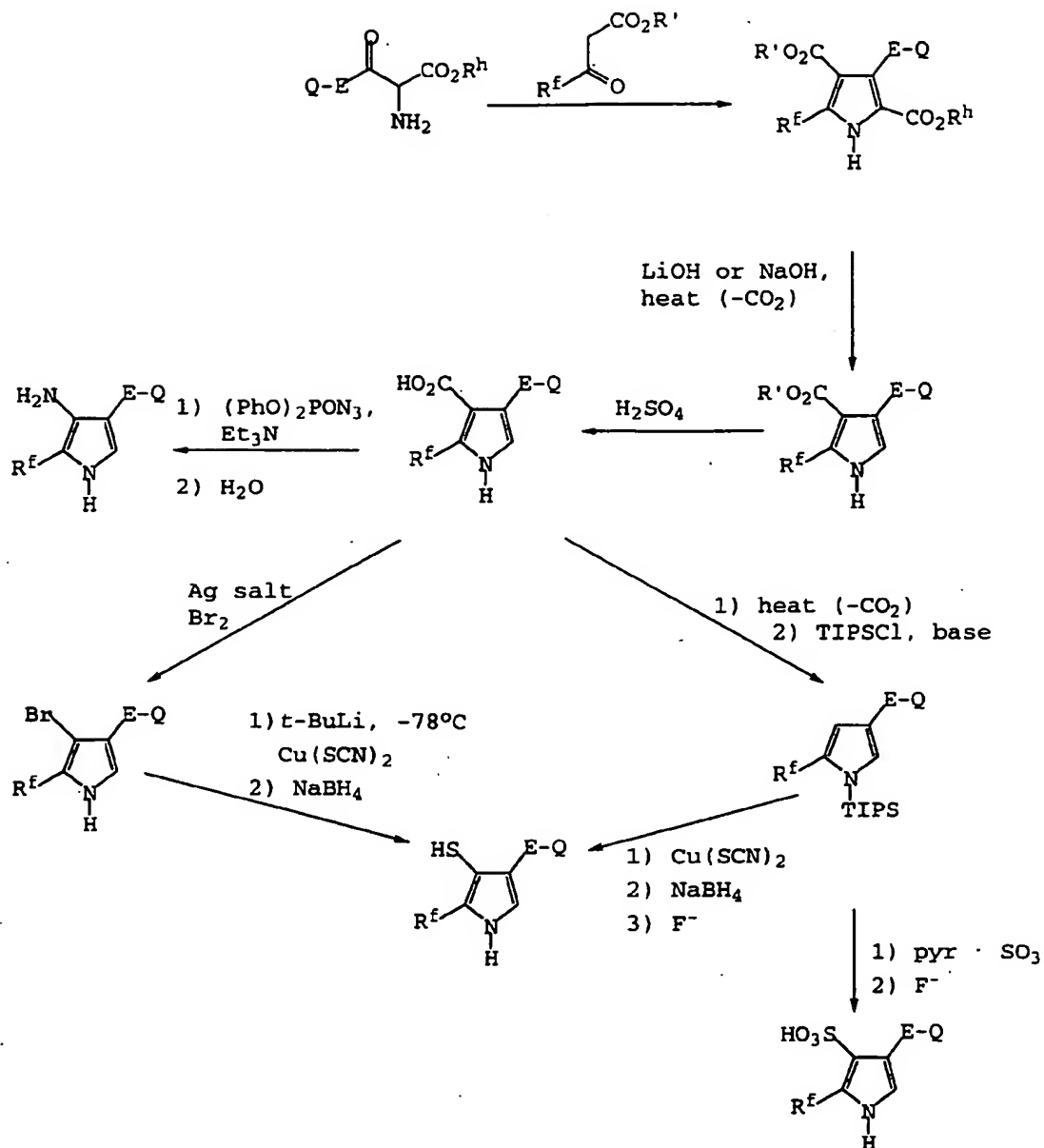
carboxylic acids can be used to prepare the 3-mercapto and 3-sulfonic acid derivatives. The Hunsdiecker procedure can be used to prepare the 3-bromopyrroles. Halogen metal exchange with *t*-BuLi at low temperature followed by quenching with

5 copper isocyanate should introduce an isocyanate group at C-3. This intermediate can be reduced with sodium borohydride to afford the 3-mercaptopyrroles. Alternatively, the carboxylic acids can be decarboxylated to afford pyrroles which can be N-protected with a bulky protecting group such as

10 triisopropylsilyl (TIPS). This bulky group directs electrophilic substitution to C-3 of the pyrrole ring. Thus, reaction with copper isocyanate followed by sodium borohydride reduction and then fluoride induced TIPS deprotection can afford 3-mercaptopyrroles. Sulfonation of N-protected pyrrole

15 with pyridine sulfur trioxide complex can again be directed to C-3 of the pyrrole to afford, after TIPS deprotection, the 3-sulfonic acids.

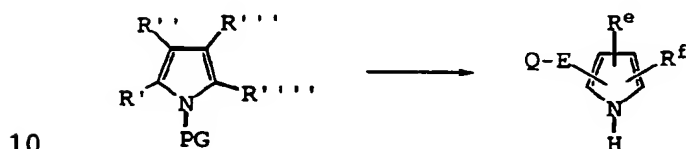
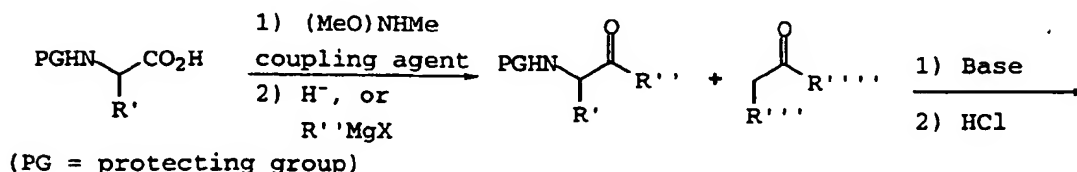
Scheme 4



5 Another general method of pyrrole synthesis that can be
 used to prepare compounds of the present invention is shown in
 Scheme 5. This approach (Cushman et. al. *J. Org. Chem.* **1996**,
 61, 4999) uses N-protected α -aminoketones and N-protected α -
 aminoaldehydes which are readily available from α -amino acids
 10 by initial preparation of the N-methoxy-N-methylamides
 followed by addition of an alkyl Grignard reagent (to produce
 ketones) or by reduction with a hydride reducing agent such as
 lithium aluminum hydride or diisobutylaluminum hydride. These

aldehydes and ketones can be allowed to react with the enolates of additional ketones to afford intermediate aldol addition products which under acidic conditions cyclize to form pyrroles. The reacting partners in this approach can be of wide scope and can be chosen so that one skilled in the art will be able to prepare varied pyrroles.

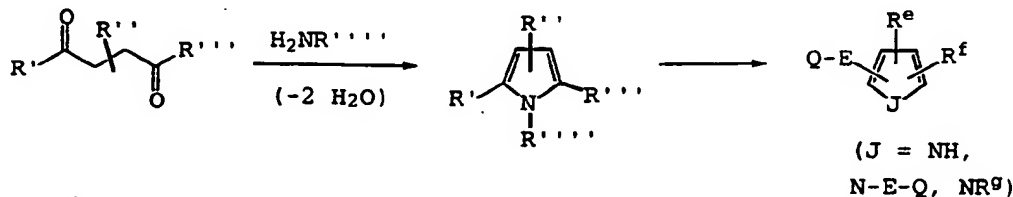
Scheme 5



10

Another very general method of pyrrole synthesis useful for preparing compounds of the present invention is the Paal-Knorr reaction shown in Scheme 6. This reaction involves the reacting 1,4-diketones or 1,4-ketoaldehydes with primary amines to afford pyrroles. The starting 1,4-diketones and 1,4-ketoaldehydes can be prepared using standard enolate chemistry or by other procedures which are familiar to those skilled in the art of organic synthesis. The reaction is of wide scope and the starting materials can be chosen so that a variety of pyrroles can be prepared.

Scheme 6



25

In Scheme 7 is shown how the compounds of Schemes 1-6 wherein R^e is a carboxylic ester group can be converted into compounds containing the Z-A-B residue. For the amide linker (Formula I, Z = -CONH-), when R^e = carboalkoxy, it can be hydrolyzed to the acid under either basic or acidic conditions depending on the substitution pattern, as described previously. Formation of the acid chloride with thionyl chloride followed by the addition of an appropriate amine H₂N-A-B can afford the amide-linked compounds. Alternatively, the acid can be combined with amine H₂N-A-B in the presence of a suitable peptide coupling agent, such as BOP-Cl, HBTU or DCC. In another method the ester can be directly coupled with an aluminum reagent, prepared by the addition of trimethylaluminum to the amine H₂N-A-B.

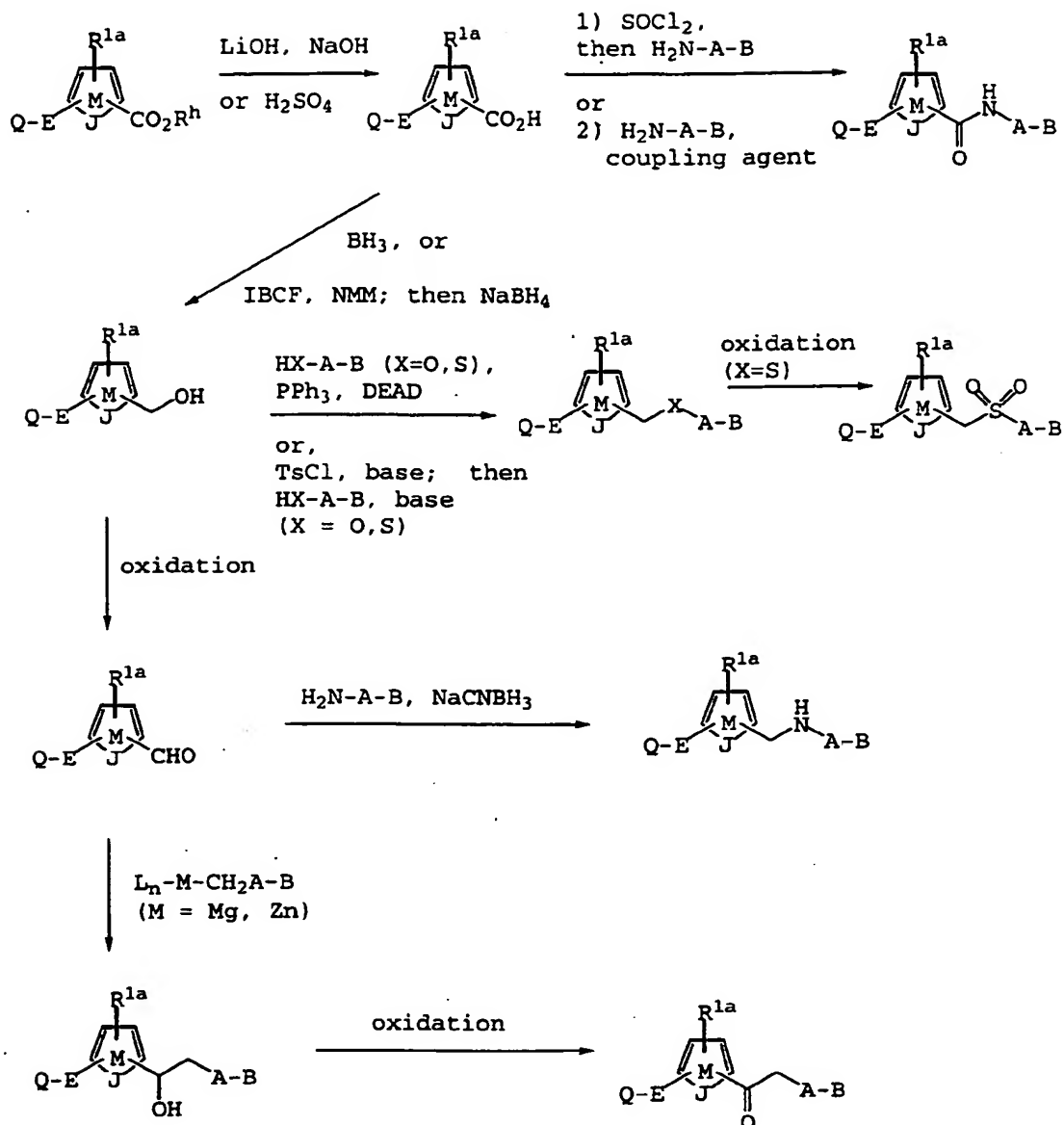
To form ether- or thioether-linked compounds of Formula I (Z = -CH₂O-, -CH₂S-) the acid can be reduced to the alcohol. Preferred procedures for this transformation are reduction with borane THF complex, or a procedure involving the reduction of the mixed anhydride with sodium borohydride (IBCF=isobutyl chloroformate and NMM=N-methylmorpholine). Completion of the ether and thioether linked compounds of Formula I can readily be accomplished by the Mitsunobu protocol with an appropriate phenol, thiophenol or hydroxy- or mercaptoheterocycle HX-A-B (X = O, S) (Formula I, A = aryl or heteroaryl). Other ethers or thioethers (X = O, S) can be prepared following initial conversion of the alcohol to a suitable leaving group, such as tosylate. Where X = S, thioethers can be further oxidized to prepare the sulfones (Formula I, Z = -CH₂SO₂-).

To prepare the amine-linked compounds of Formula I (Z = -CH₂NH-) the alcohol can be oxidized to the aldehyde by a number of procedures, two preferred methods of which are the Swern oxidation and oxidation with pyridinium chlorochromate (PCC). Alternatively, the aldehyde may be directly prepared by direct formylation of the pyrrole ring by the Vilsmeier-Haack procedure in certain cases, as described in previous schemes. Reductive amination of the aldehyde

with an appropriate amine H_2N-A-B and sodium cyanoborohydride can then afford the amine linked compounds.

- The aldehyde also can be used to prepare the ketone-linked compounds of Formula I ($Z = -COCH_2-$). Treatment with
- 5 an organometallic species can afford the alcohol. The organometallic species (wherein $M =$ magnesium or zinc) can preferably be prepared from the corresponding halide by treatment with metallic magnesium or zinc. These reagents should readily react with aldehydes to afford alcohols.
- 10 Oxidation of the alcohol by any of a number of procedures, such as the Swern oxidation or PCC oxidation, can afford the ketones-linked compounds.

Scheme 7

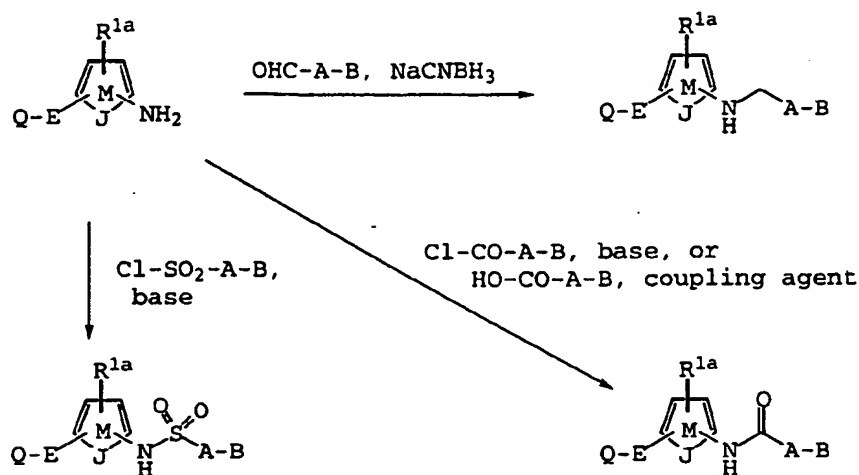


- 5 Additional compounds of Formula I in which the linking group m/z contains a nitrogen atom attached to ring M can be prepared by the procedures described in Scheme 8. The amines can be converted to sulfonamides (Formula I, $m/z-NHSO_2-$) by treatment with an appropriate sulfonyl chloride $B-A-SO_2Cl$ in the presence of a base such as triethylamine. The amines can be converted into amides (Formula I, $Z = -NHCO-$) by treatment with an appropriate acid chloride $Cl-CO-A-B$ in the presence of a base or by treatment with an appropriate carboxylic acid $HO-$
- 10

CO-A-B in the presence of a suitable peptide coupling agent, such as DCC, HBTU or BOP. The amines can also be converted into amine-linked compounds (Formula I, $Z = -NHCH_2-$) by reductive amination with an appropriate aldehyde OHC-A-B.

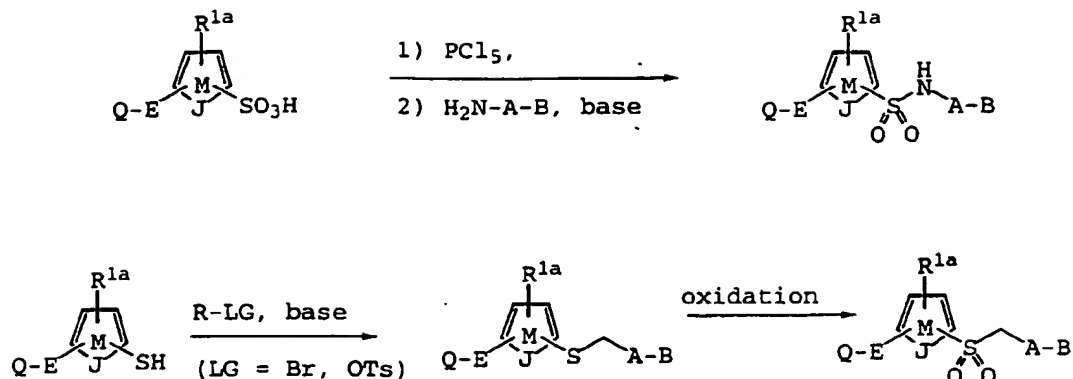
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Scheme 8



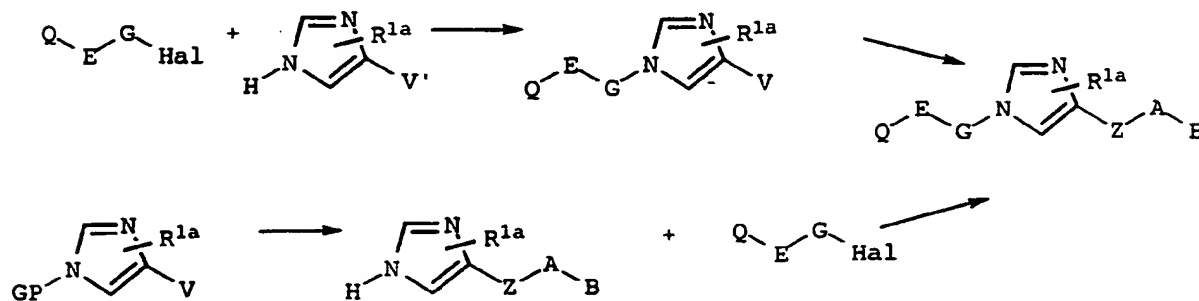
- 10 Additional compounds of Formula I in which the linking group Z contains a sulfur atom attached to ring M can be prepared by the procedures described in Scheme 9. Treatment of sulfonic acids with phosphorous pentachloride followed by treatment with an appropriate amine H_2N-A-B can afford
- 15 sulfonamide-linked compounds (Formula I, $Z = -SO_2NH-$). The thiols can be alkylated with a suitable alkylating reagent in the presence of a base to afford thioethers (Formula I, $Z = -SCH_2-$). These compounds can be further oxidized by a variety of reagents to afford the sulfone-linked compounds (Formula I,
- 20 $Z = -SO_2CH_2-$).

Scheme 9



- 5 Compounds of Formula I wherein ring M is an imidazole can be formed using procedures described in Schemes 10-16. N-Substituted imidazole derivatives can be made by the general procedure shown in Scheme 10, wherein V' is either V or a precursor of $(\text{CH}_2)_n\text{V}$, V is nitro, amino, thio, hydroxy, sulfonic acid, sulfonic ester, sulfonyl chloride, ester, acid, or
- 10 acid, sulfonic ester, sulfonyl chloride, ester, acid, or halide, n is 0 and 1, and PG is either a hydrogen or a protecting group. Substitution can be achieved by coupling an imidazole with a halogen containing fragment Q-E-G-Hal in the presence of a catalyst, such as base, Cu/CuBr/base, or
- 15 Pd/base, followed by conversion of V' to $(\text{CH}_2)_n\text{V}$. Then, Q can be converted to D, and finally V can be converted to -Z-A-B following the procedures outlined in Schemes 7-9. Alternatively, V can be converted to Z-A-B followed by deprotection of N. This product can then be coupled as before
- 20 to obtain the desired imidazole.

Scheme 10

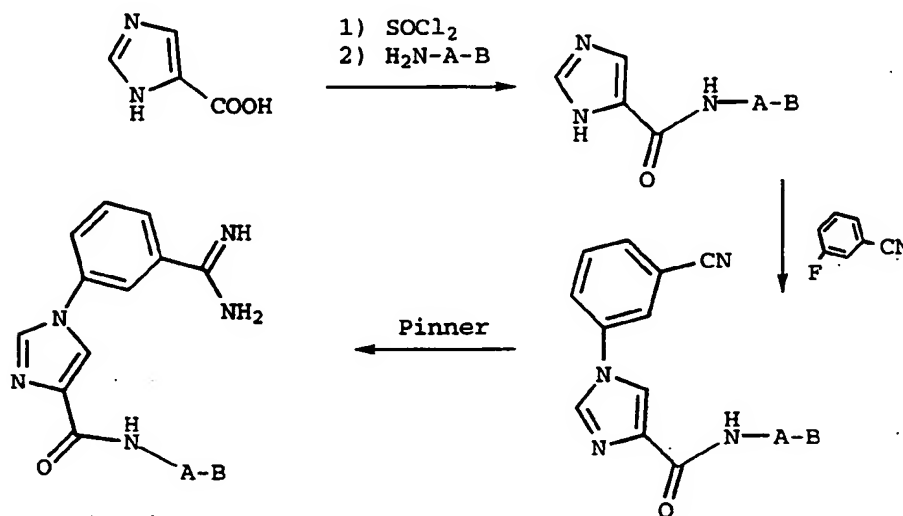


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One way to make amidino-phenyl-imidazole derivatives is shown in Scheme 11. 4-Imidazole carboxylic acid can be treated with thionyl chloride and then coupled with H₂N-A-B in the presence of a base and then be heated with 3-fluorobenzonitrile in the presence of a base. The Pinner reaction using standard procedures known to those of skill in the art can be used to form the amidino group.

Scheme 11

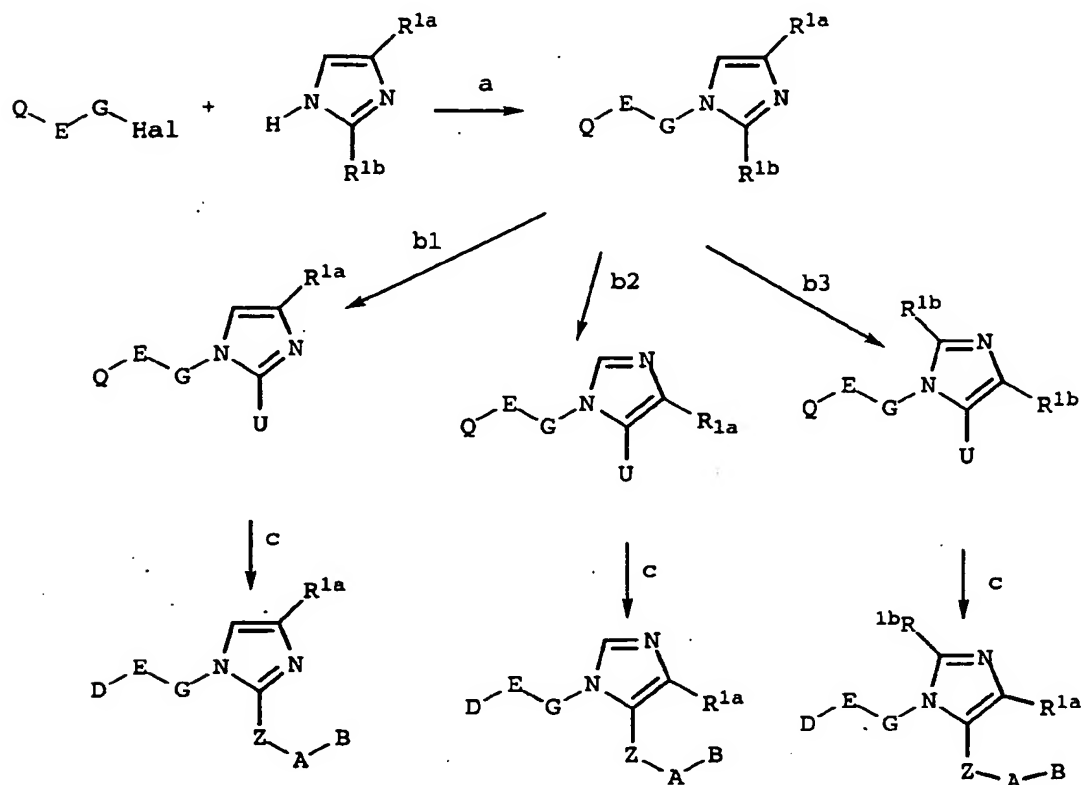
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1,2-Disubstituted and 1,5-disubstituted imidazole derivatives can be made by the general procedures described in Scheme 12, wherein R^{1b} is either a hydrogen or an alkyl group and U is aldehyde, ester, acid, amide, amino, thiol, hydroxy, sulfonic acid, sulfonic ester, sulfonyl chloride, or methylene halide. Step a involves coupling in the presence of a catalyst, such as base, Cu/CuBr/base, or Pd/base. When R^{1b} is a hydrogen, it can be deprotonated with a lithium base and trapped by formate, formamide, carbon dioxide, sulfonyl chloride (sulfur dioxide and then chlorine), or isocyanate to give 1,2-disubstituted imidazoles (Route b1). Also, in Route b1 when R^{1b} is CH₃, it can be oxidized with SeO₂, MnO₂, NaIO₄/cat. RhCl₃, or NBS to form U. When R^{1b} is hydrogen, sequential deprotonation and quenching with a lithium base and trimethylsilyl chloride, followed by a second deprotonation with a lithium base and quenching with formate, formamide,

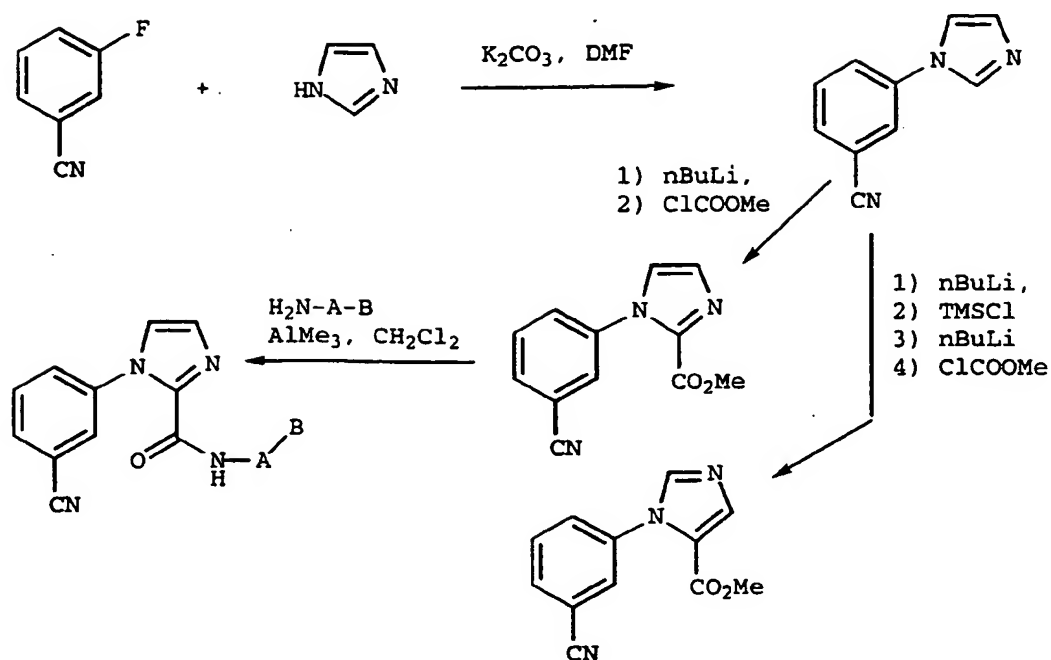
carbon dioxide, sulfonyl chloride (sulfur dioxide and then chlorine), or isocyanate can afford 1,5-disubstituted imidazoles (Route b2). When R^{1b} is not hydrogen, the procedure of Route b2 can again be used to form 1,5-disubstituted imidazoles (Route b3).

Scheme 12



A preferred way of making 1,2-disubstituted and 1,5-disubstituted imidazole derivatives is shown in Scheme 13. Imidazole can be heated with 3-fluorobenzonitrile in the presence of a base. The coupled product can then be treated with an alkyl lithium base and quenched with ClCO₂Me to give the 1,2-disubstituted compound. Further treatment with a solution prepared of H₂N-A-B in trimethylaluminum can give the amide, which can be further modified via the Pinner reaction to form the desired compound. The 1,5-disubstituted compounds can be made using the same procedure, except that the initial anion is protected and a second anion is formed which is then quenched as noted above. Further modifications can follow the same procedures as the 1,2-disubstituted compounds.

Scheme 13

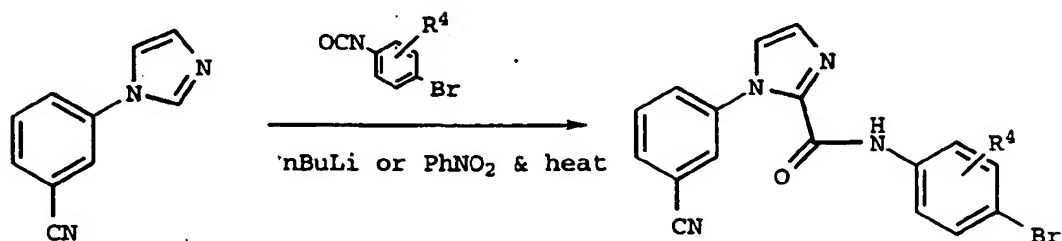


5

Another way of making 1,2-disubstituted imidazole derivatives is described in Scheme 14. By reacting an N-substituted imidazole with a cyanate, the amide can be obtained. This amide can then be coupled with group B as will be described later.

10

Scheme 14



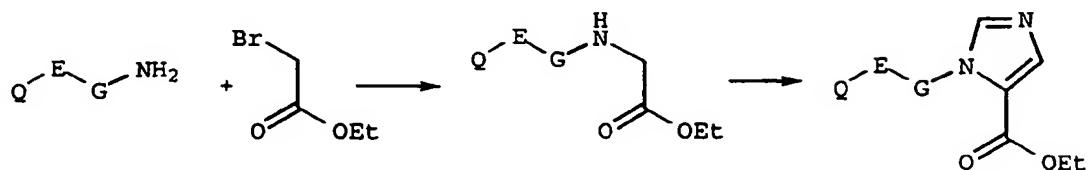
15

Another means of making 1,5-disubstituted imidazole derivatives is described in Scheme 15. Alkylation with 2-bromoethylacetate and subsequent reaction with Gold's reagent in the presence of a base, such as NaOMe, or LDA, can form

ester substituted imidazoles which can be further modified as previously described.

Scheme 15

5

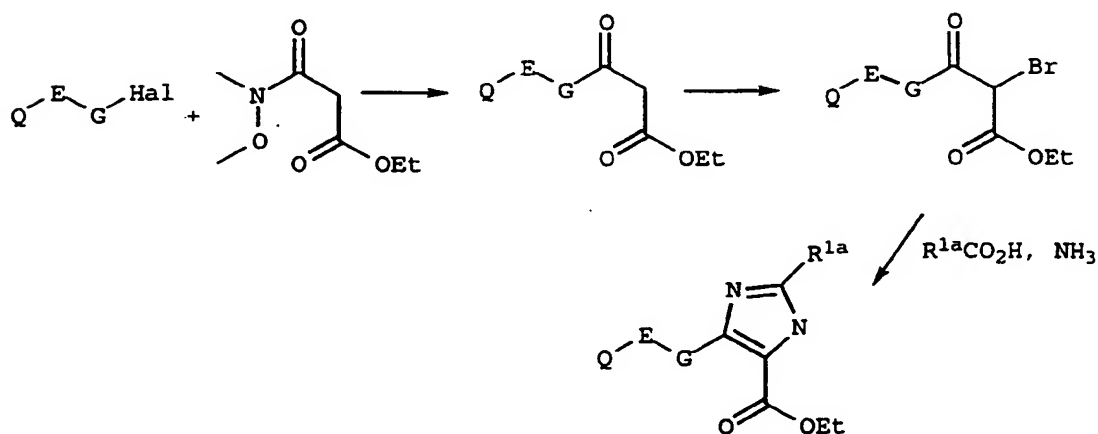


A general procedure to make 2,4,5-trisubstituted or 4,5-disubstituted imidazole derivatives is shown in Scheme 16.

10 After metal halogen exchange of the Q-E-G fragment, it can be reacted with the amide shown, brominated with NBS and cyclized with excess NH_3 and $\text{R}^{1a}\text{CO}_2\text{H}$ to afford an imidazole. This can then be modified as before.

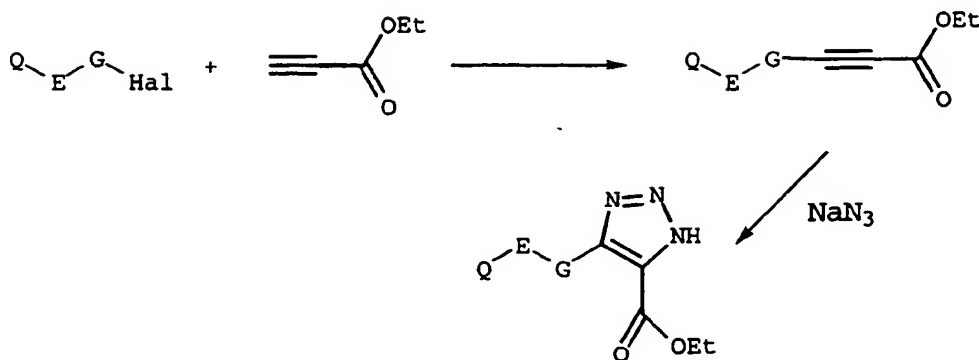
15

Scheme 16



20 A general procedure to make 4,5-disubstituted triazole derivatives is described in Scheme 17. Ethyl propiolate can be substituted in the presence of CuI/Pd and then reacted with NaN_3 to form a triazole. The triazole can be converted as described previously.

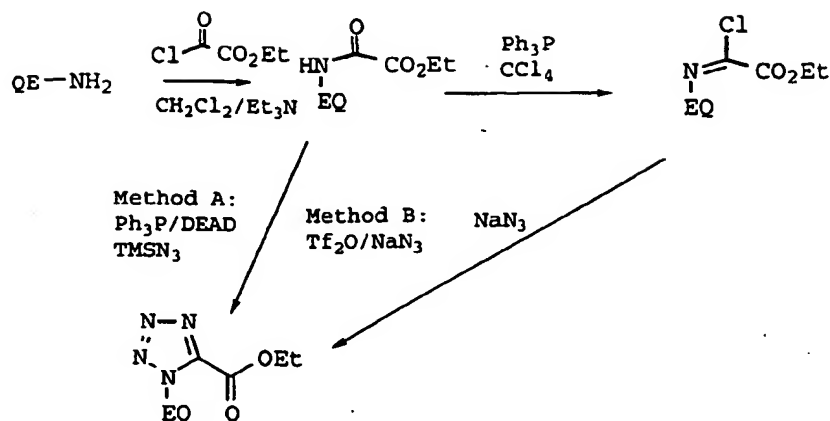
Scheme 17



5 The tetrazole compounds of the present invention where Z
 is -CONH- can be prepared as exemplified in Scheme 18. An
 appropriately substituted amine can be acylated with ethyl
 oxalyl chloride. The resulting amide can be converted to the
 tetrazole either by the methods described by Duncia (*J. Org.*
 10 *Chem.* **1991**, 2395-2400) or Thomas (*Synthesis* **1993**, 767-768).
 The amide can be converted to the iminoyl chloride first and
 the reacted with NaN₃ to form the 5-carboethoxytetrazole (*J.*
Org. Chem. **1993**, 58, 32-35 and *Bioorg. & Med. Chem. Lett.*
1996, 6, 1015-1020). The 5-carboethoxytetrazole can then be
 15 further modified as described in Scheme 7.

The tetrazole compounds of the present invention where Z
 is -CO- can also be prepared via iminoyl chloride (*Chem. Ber.*
1961, 94, 1116 and *J. Org. Chem.* **1976**, 41, 1073) using an
 appropriately substituted acyl chloride as starting material.
 20 The ketone-linker can be reduced to compounds wherein Z is
 alkyl.

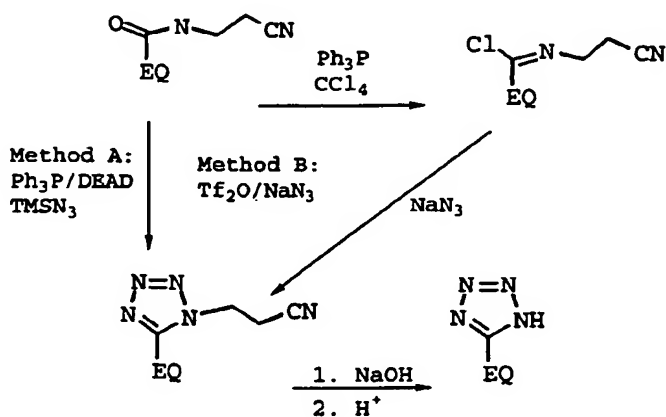
Scheme 18



5 The methods described in Scheme 18 can also be used to synthesize compounds where the E-Q is linked to the carbon atom of the tetrazole as shown in Scheme 19. The 5-substituted tetrazole can then be alkylated or acylated to give the desired products.

10

Scheme 19



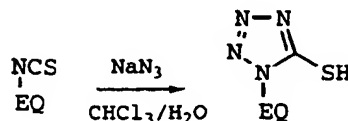
15 The tetrazole compounds of the present invention wherein Z is -SO₂NH-, -S-, -S(O)-, SO₂- can be prepared from the thiol prepared as shown in Scheme 20. Appropriately substituted thioisocyanate can be reacted with sodium azide to give the 5-thiotetrazole (*J. Org. Chem.* **1967**, 32, 3580-3592). The thio-

20 compound can be modified as described in Scheme 9.

The tetrazole compounds of the present invention wherein Z is -O- can be prepared via the same method described in

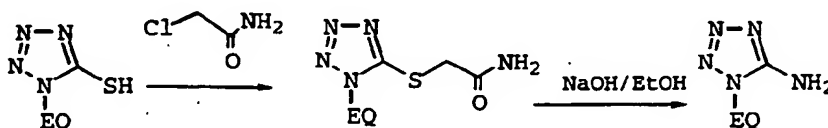
Scheme 20 by using appropriately substituted isocyanate as the starting material. The hydroxy compound can be modified similarly to the thiols described in Scheme 9.

5

Scheme 20

The tetrazole compounds of the present invention wherein
 10 Z is -NH-, -NHCO-, -NHSO₂- can be prepared from 5-aminotetrazole, which can be prepared by Smiles Rearrangement as shown in Scheme 21. The thio-compound prepared as described in Scheme 20 can be alkylated with 2-chloroacetamide. The resulting compound can then be refluxed
 15 in ethanolic sodium hydroxide to give the corresponding 5-amino-tetrazole (*Chem. Pharm. Bull.* **1991**, 39, 3331-3334). The resulting 5-amino-tetrazole can then be alkylated or acylated to form the desired products.

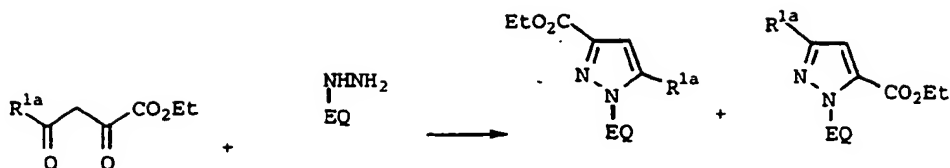
20

Scheme 21

Pyrazoles of Formula I (such as those described in Scheme
 25 22) can be prepared by the condensation of an appropriately substituted hydrazine with a variety of diketo esters. Condensations of this type typically afford a mixture of pyrazole regioisomers which can be effectively separated via silica gel column chromatography. The esters can be converted
 30 to Z-A-B as previously described.

Alternatively, if in Scheme 22, the starting diketone contains CH₃ in place of CO₂Et, then the resulting methyl pyrazole can be separated and oxidized as in Route b1 in Scheme 12 to form the pyrazole carboxylic acid.

Scheme 22

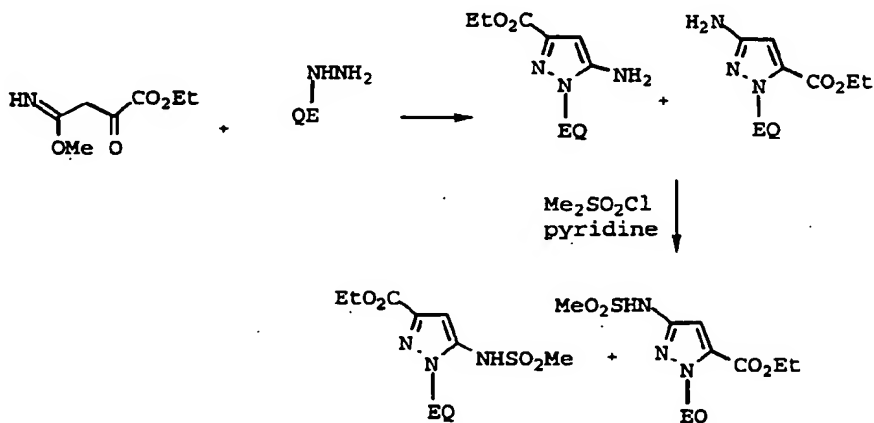


5

When ketoimides are used for condensations with hydrazines the corresponding pyrazole amino esters are obtained (Scheme 23). Conversion of these intermediates to the final compounds of formula I can then be accomplished by the protection of the amino functionality with a suitable protecting group or by derivatization (e.g. sulfonamide) and then modifying the ester as previously noted.

10

Scheme 23

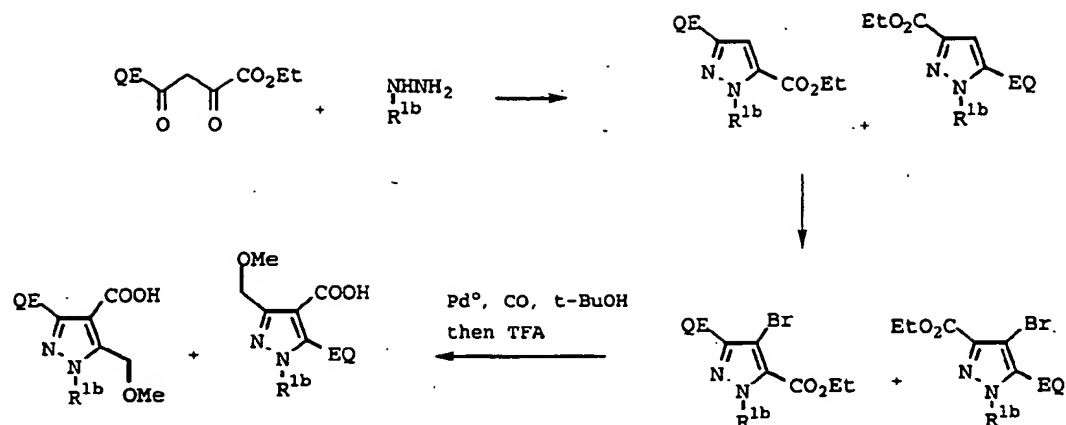


15

As shown in Scheme 24, pyrazoles wherein the 4-position is substituted can be prepared by bromination (bromine or NBS in either dichloromethane or acetic acid) of the initial pyrazole. Conversion of 4-bromo-pyrazole to 4-carboxylic acid pyrazole can be accomplished by a number of methods commonly known to those in the art of organic synthesis. Further manipulations as previously described can afford pyrazoles of the present invention.

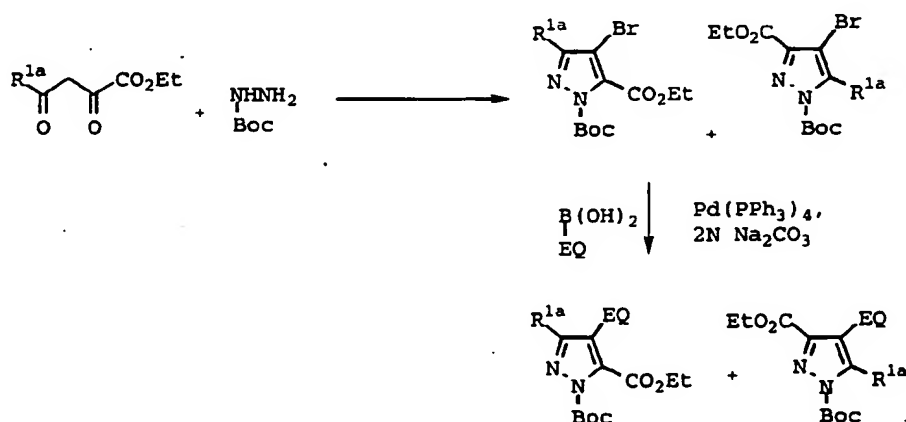
25

Scheme 24



Pyrazoles can also be prepared according to method described in Scheme 25. The bromo-pyrazoles are formed as in Scheme 24. QE can then be coupled using palladium catalysed Suzuki cross-coupling methodology. Further modification is achieved as previously described.

Scheme 25

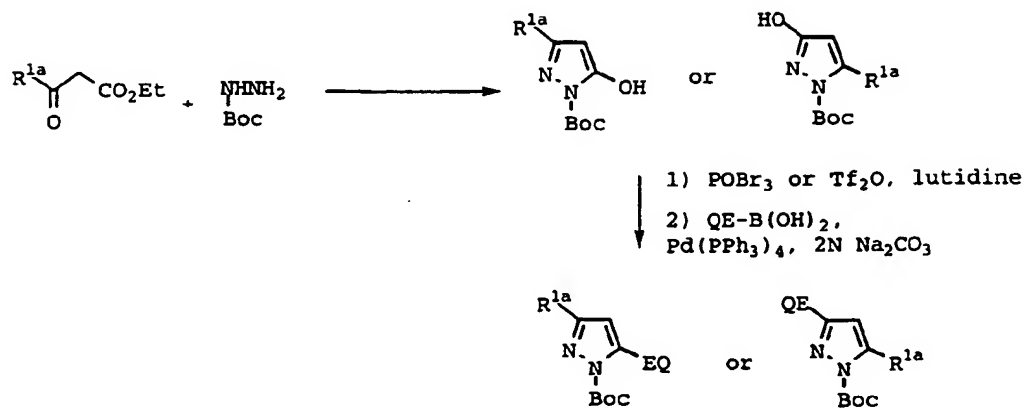


5-substituted phenylpyrazoles can be prepared by the method shown in Scheme 26. Conversion of the 5-hydroxy pyrazole to its triflate (triflic anhydride, lutidine in dichloromethane) or bromide (POBr₃) followed by palladium Suzuki cross-coupling with an appropriately substituted phenylboronic acid should then afford 5-substituted pyrazoles. Conversion of this intermediate to the 4-bromo derivative

followed by its carbonylation as described in Scheme 24 should then afford the appropriate ester which can be further afford the compounds of formula I.

5

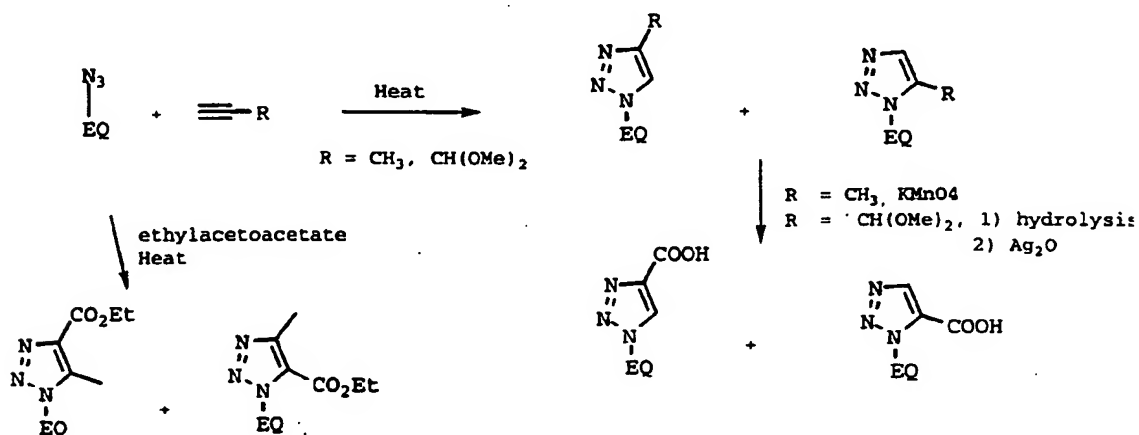
Scheme 26



1-Substituted-1,2,3-triazoles of the present invention can be prepared by the treatment of an appropriately substituted azide with a variety of dipolarophiles (*Tetrahedron* **1971**, 27, 845 and *J. Amer. Chem. Soc.* **1951**, 73, 1207) as shown in Scheme 27. Typically a mixture of regioisomers are obtained which can be easily separated and elaborated to the triazole carboxylic acids. Further transformations as previously described can then afford the compounds of the present invention.

20

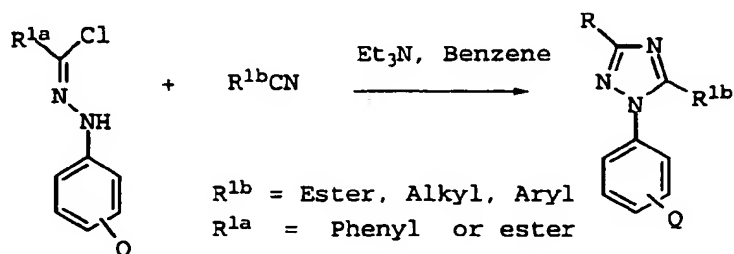
Scheme 27



1,2,4-Triazoles of the present invention can be obtained by the methodology of Huisgen et al (*Liebigs Ann. Chem.* **1962**, 653, 105) by the cycloaddition of nitriliminium species (derived from the treatment of triethylamine and chloro
 5 hydrazone) and an appropriate nitrile dipolarophile (Scheme 28). This methodology provides a wide variety of 1,2,4 triazoles with a varied substitution pattern at the 1, 3, and 5 positions.

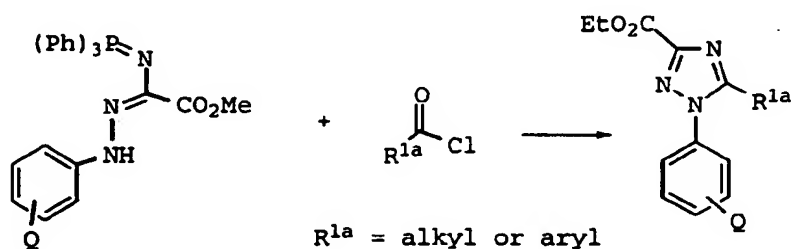
10

Scheme 28



1,2,4 Triazoles can also be prepared by the methodology
 15 of Zecchi et al (*Synthesis* **1986**, 9, 772) by an aza Wittig condensation (Scheme 29).

Scheme 29

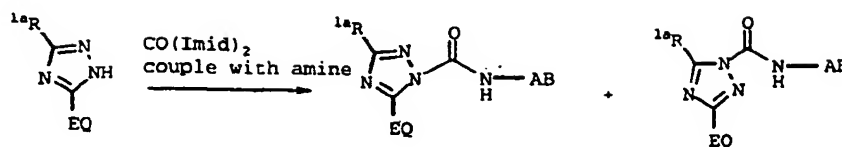


20

1,2,4-Triazoles wherein the -E-D(Q) substituent is at the
 5-position of the triazole can be obtained as shown in Scheme
 30.

25

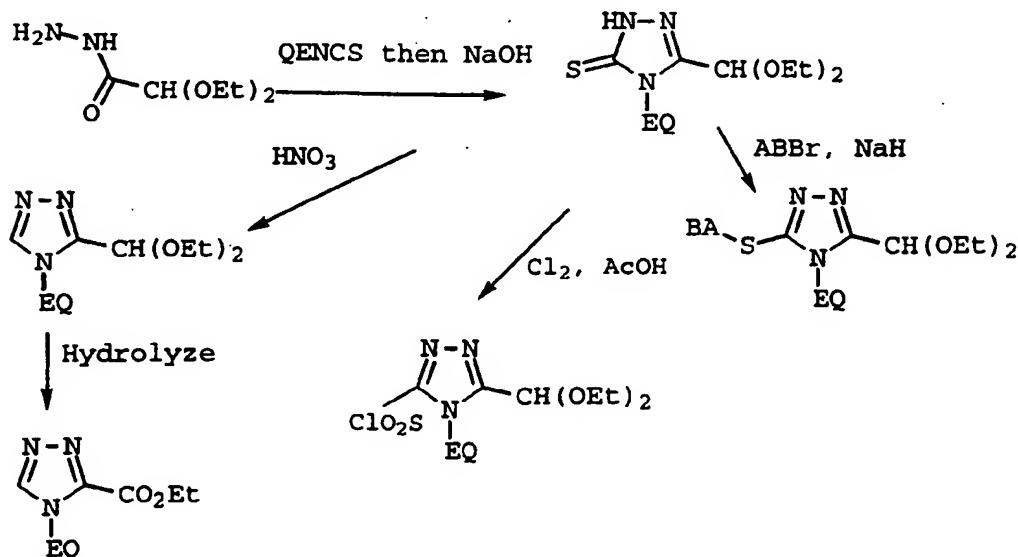
Scheme 30



5 1,3,4-Triazoles of the present invention can be obtained
 via the methodology of Moderhack et al (*J. Prakt. Chem.* 1996,
 338, 169). As shown in Scheme 31, this reaction involves the
 condensation of a carbazide with an appropriately substituted
 commercially available thioisocyanate to form the cyclic
 10 thiourea derivative. Alkylation or nucleophilic displacement
 reactions on the thiono-urea intermediate can then afford a
 thio-alkyl or aryl intermediate which can be hydrolysed,
 oxidized and decarboxylated to the 5-H 2-thio-triazole
 intermediate which can be converted to the compounds of the
 15 present invention. Alternatively the thiono-urea intermediate
 can be oxidized directly to the 2-H triazole which can then be
 converted to the ester and modified as previously described.
 The thiono-urea intermediate can also be oxidized to the
 sulfonyl chloride by methods shown previously.

20

Scheme 31

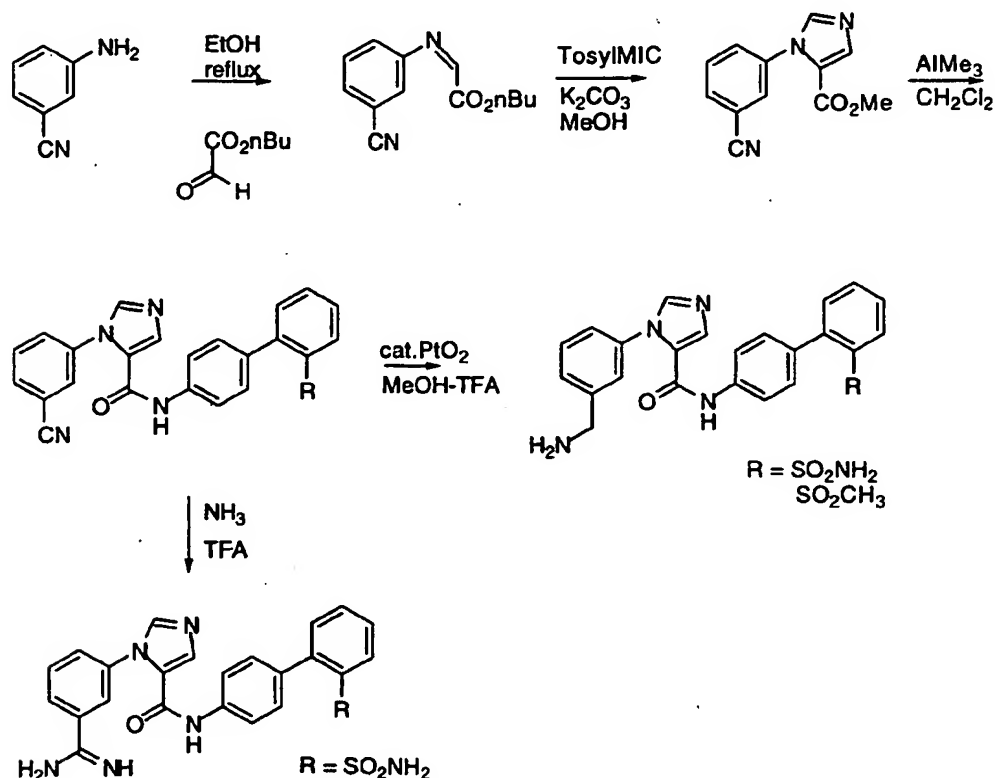


The imidazole core shown in Scheme 32 can be prepared by the condensation of 3-cyanoaniline with n-butylglyoxylate to afford the imine which can then be treated with TosylMIC in basic methanol to afford the desired imidazole compound.

- 5 Coupling of the ester under standard conditions then affords a variety of analogs which then can be further manipulated to afford e.g. the benzylamine or the benzamidines.

Scheme 32

10

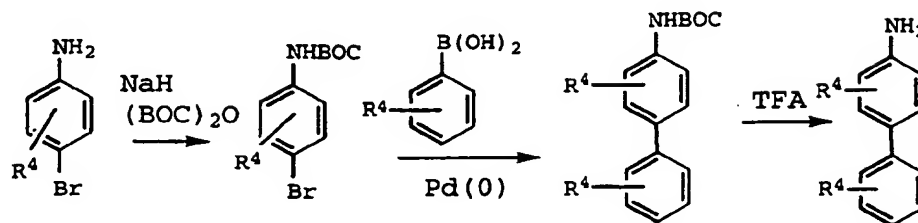


- Compounds of the present invention wherein AB is a biphenylamine or similar amine may be prepared as shown in Scheme 33. 4-Bromoaniline can be protected as Boc-derivative and coupled to a phenylboronic acid under Suzuki conditions (*Bioorg. Med. Chem. Lett.* 1994, 189). Deprotection with TFA provides the aminobiphenyl compound. Other similar amines wherein A and/or B are heterocycles can be prepared by the same method using appropriately substituted boronic acids and arylbromide. The bromoaniline can also be linked to the core
- 15
- 20

ring structures first as described above, and then undergo a Suzuki reaction to give the desired product.

Scheme 33

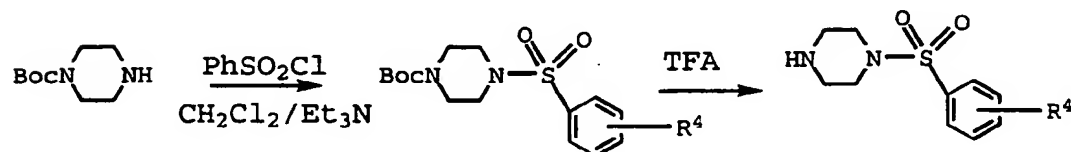
5



Compounds of the present invention wherein A-B is A-X-Y can be prepared like the piperazine derivative shown in Scheme

10 34.

Scheme 34

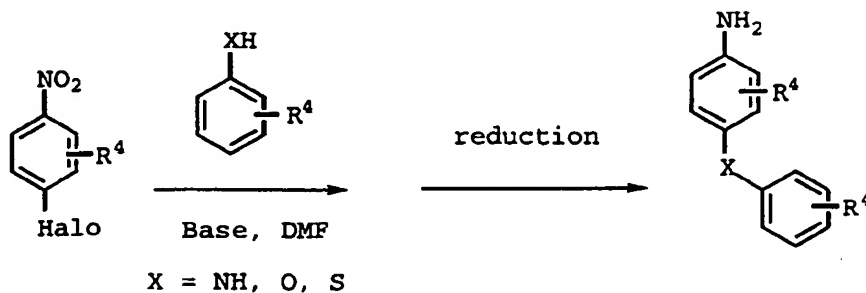


15

Scheme 35 shows how one can couple cyclic groups wherein X=NH, O, or S.

Scheme 35

20



When B is defined as X-Y, the following description applies. Groups A and B are available either through commercial sources, known in the literature or readily

synthesized by the adaptation of standard procedures known to practitioners skilled in the art of organic synthesis. The required reactive functional groups appended to analogs of A and B are also available either through commercial sources, known in the literature or readily synthesized by the adaptation of standard procedures known to practitioners skilled in the art of organic synthesis. In the tables that follow the chemistry required to effect the coupling of A to B is outlined.

10

Table A: Preparation of Amide, Ester, Urea, Sulfonamide and Sulfamide linkages between A and B.

| Rxn. No. | if A contains : | then the reactive substituent of Y is : | to give the following product A-X-Y : |
|----------|-------------------------------------------|-------------------------------------------|------------------------------------------------------------|
| 1 | A-NHR ² as a substituent | ClC(O)-Y | A-NR ² -C(O)-Y |
| 2 | a secondary NH as part of a ring or chain | ClC(O)-Y | A-C(O)-Y |
| 3 | A-OH as a substituent | ClC(O)-Y | A-O-C(O)-Y |
| 4 | A-NHR ² as a substituent | ClC(O)-CR ² R ^{2a} -Y | A-NR ² -C(O)-CR ² R ^{2a} -Y |
| 5 | a secondary NH as part of a ring or chain | ClC(O)-CR ² R ^{2a} -Y | A-C(O)-CR ² R ^{2a} -Y |
| 6 | A-OH as a substituent | ClC(O)-CR ² R ^{2a} -Y | A-O-C(O)-CR ² R ^{2a} -Y |
| 7 | A-NHR ³ as a substituent | ClC(O)NR ² -Y | A-NR ² -C(O)NR ² -Y |
| 8 | a secondary NH as part of a ring or chain | ClC(O)NR ² -Y | A-C(O)NR ² -Y |
| 9 | A-OH as a substituent | ClC(O)NR ² -Y | A-O-C(O)NR ² -Y |

| | | | |
|----|------------------------------------------------------|-------------------------------------------------------|------------------------------------------------------------------------|
| 10 | A-NHR ² as a substituent | ClSO ₂ -Y | A-NR ² -SO ₂ -Y |
| 11 | a secondary NH as part of a ring or chain | ClSO ₂ -Y | A-SO ₂ -Y |
| 12 | A-NHR ² as a substituent | ClSO ₂ -CR ² R ^{2a} -Y | A-NR ² -SO ₂ -CR ² R ^{2a} -Y |
| 13 | a secondary NH as part of a ring or chain | ClSO ₂ -CR ² R ^{2a} -Y | A-SO ₂ -CR ² R ^{2a} -Y |
| 14 | A-NHR ² as a substituent | ClSO ₂ -NR ² -Y | A-NR ² -SO ₂ -NR ² -Y |
| 15 | a secondary NH as part of a ring or chain | ClSO ₂ -NR ² -Y | A-SO ₂ -NR ² -Y |
| 16 | A-C(O)Cl | HO-Y as a substituent | A-C(O)-O-Y |
| 17 | A-C(O)Cl | NHR ² -Y as a substituent | A-C(O)-NR ² -Y |
| 18 | A-C(O)Cl | a secondary NH as part of a ring or chain | A-C(O)-Y |
| 19 | A-CR ² R ^{2a} C(O)Cl | HO-Y as a substituent | A-CR ² R ^{2a} C(O)-O-Y |
| 20 | A-CR ² R ^{2a} C(O)Cl | NHR ² -Y as a substituent | A-CR ² R ^{2a} C(O)-NR ² -Y |
| 21 | A-CR ² R ^{2a} C(O)Cl | a secondary NH as part of a ring or chain | A-CR ² R ^{2a} C(O)-Y |
| 22 | A-SO ₂ Cl | NHR ² -Y as a substituent | A-SO ₂ -NR ² -Y |
| 23 | A-SO ₂ Cl | a secondary NH as part of a ring or chain | A-SO ₂ -Y |
| 24 | A-CR ² R ^{2a} SO ₂ Cl | NHR ² -Y as a substituent | A-CR ² R ^{2a} SO ₂ -NR ² -Y |

| | | | |
|----|----------------------|-------------------------------------------------|----------------------|
| 25 | $A-CR^2R^{2a}SO_2Cl$ | a secondary NH as part of a ring or chain | $A-CR^2R^{2a}SO_2-Y$ |
|----|----------------------|-------------------------------------------------|----------------------|

The chemistry of Table A can be carried out in aprotic solvents such as a chlorocarbon, pyridine, benzene or toluene, at temperatures ranging from $-20^\circ C$ to the reflux point of the solvent and with or without a trialkylamine base.

Table B: Preparation of ketone linkages between A and B.

| Rxn. No. | if A contains : | then the reactive substituent of Y is : | to give the following product A-X-Y : |
|----------|----------------------|-----------------------------------------|---------------------------------------|
| 1 | $A-C(O)Cl$ | $BrMg-Y$ | $A-C(O)-Y$ |
| 2 | $A-CR^2R^{2a}C(O)Cl$ | $BrMg-Y$ | $A-CR^2R^{2a}C(O)-Y$ |
| 3 | $A-C(O)Cl$ | $BrMgCR^2R^{2a}-Y$ | $A-C(O)CR^2R^{2a}-Y$ |
| 4 | $A-CR^2R^{2a}C(O)Cl$ | $BrMgCR^2R^{2a}-Y$ | $A-CR^2R^{2a}C(O)CR^2R^{2a}-Y$ |

The coupling chemistry of Table B can be carried out by a variety of methods. The Grignard reagent required for Y is prepared from a halogen analog of Y in dry ether, dimethoxyethane or tetrahydrofuran at $0^\circ C$ to the reflux point of the solvent. This Grignard reagent can be reacted directly under very controlled conditions, that is low temperature ($-20^\circ C$ or lower) and with a large excess of acid chloride or with catalytic or stoichiometric copper bromide-dimethyl sulfide complex in dimethyl sulfide as a solvent or with a variant thereof. Other methods available include transforming the Grignard reagent to the cadmium reagent and coupling according to the procedure of Carson and Prout (Org. Syn. Col. Vol. 3 (1955) 601) or a coupling mediated by $Fe(acac)_3$ according to Fiandanese et al. (Tetrahedron Lett., (1984) 4805), or a coupling mediated by manganese (II) catalysis (Cahiez and Laboue, Tetrahedron Lett., 33(31), (1992) 4437).

Table C: Preparation of ether and thioether linkages between A and B

| Rxn. No. | if A contains : | then the reactive substituent of Y is : | to give the following product A-X-Y : |
|----------|---------------------------------------|-----------------------------------------|---------------------------------------|
| 1 | A-OH | Br-Y | A-O-Y |
| 2 | A-CR ² R ^{2a} -OH | Br-Y | A-CR ² R ^{2a} O-Y |
| 3 | A-OH | Br-CR ² R ^{2a} -Y | A-OCR ² R ^{2a} -Y |
| 4 | A-SH | Br-Y | A-S-Y |
| 5 | A-CR ² R ^{2a} -SH | Br-Y | A-CR ² R ^{2a} S-Y |
| 6 | A-SH | Br-CR ² R ^{2a} -Y | A-SCR ² R ^{2a} -Y |

The ether and thioether linkages of Table C can be prepared by reacting the two components in a polar aprotic solvent such as acetone, dimethylformamide or dimethylsulfoxide in the presence of a base such as potassium carbonate, sodium hydride or potassium t-butoxide at temperature ranging from ambient temperature to the reflux point of the solvent used.

Table D: Preparation of -SO- and -SO₂- linkages from thioethers of Table C.

| Rxn. No. | if the starting material is : | and it is oxidized with Alumina (wet)/ Oxone (Greenhalgh, Synlett, (1992) 235) the product is : | and it is oxidized with m-chloroperbenzoic acid (Sato et al., Chem. Lett. (1992) 381), the product is : |
|----------|---------------------------------------|-------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| 1 | A-S-Y | A-S(O)-Y | A-SO ₂ -Y |
| 2 | A-CR ² R ^{2a} S-Y | A-CR ² R ^{2a} S(O)-Y | A-CR ² R ^{2a} SO ₂ -Y |
| 3 | A-SCR ² R ^{2a} -Y | A-S(O)CR ² R ^{2a} -Y | A-SO ₂ CR ² R ^{2a} -Y |

The thioethers of Table C serve as a convenient starting material for the preparation of the sulfoxide and sulfone analogs of Table D. A combination of wet alumina and oxone can provide a reliable reagent for the oxidation of the

thioether to the sulfoxide while m-chloroperbenzoic acid oxidation will give the sulfone.

Table E: Methods of Preparing Group E

5

| Rxn | Q | D is to be | then a transformation that may be used is : |
|-----|--------------------|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | -CN | -C(=NH)NH ₂ | $\text{E}-\text{C}\equiv\text{N} \xrightarrow[\text{ii) NH}_3\text{OAc, MeOH}]{\text{i) HCl MeOH}} \text{E}-\text{C} \begin{matrix} \text{NH}_2 \\ \diagup \\ \text{=NH} \end{matrix}$ |
| 2 | -CN | -CH ₂ NH ₂ | $\text{E}-\text{C}\equiv\text{N} \xrightarrow[\text{Et}_2\text{O}]{\text{LiAlH}_4} \text{E}-\text{CH}_2\text{NH}_2$ |
| 3 | -CO ₂ H | -CH ₂ NH ₂ | $\text{E}-\text{C} \begin{matrix} \text{O} \\ \parallel \\ \text{OH} \end{matrix} \xrightarrow[\text{ii) MsCl, Et}_3\text{N, CH}_2\text{Cl}_2]{\text{i) iBuOC(O)Cl, NMM, THF then NaBH}_4, \text{H}_2\text{O/THF}} \text{E}-\text{CH}_2\text{NH}_2$ <p>iii) NaN₃, DMF iv) SnCl₂, MeOH</p> |
| 4 | -CO ₂ H | -NH ₂ | $\text{E}-\text{C} \begin{matrix} \text{O} \\ \parallel \\ \text{OH} \end{matrix} \xrightarrow[\text{iii) HCl, Et}_2\text{O}]{\text{i) iBuOC(O)Cl, NMM, THF then NaN}_3 \text{ and heat}} \text{E}-\text{NH}_2$ <p>ii) tBuOH, reflux</p> |

In Table E several methods of transforming a functional group Q into group D of Formula 1 are shown. While not all possible functional groups for Q and D are listed and the synthetic methods suggested are not comprehensive, Table E is meant to illustrate strategies and transformations available to a practitioner skilled in the art of organic synthesis for preparing compounds of Formula 1. In reaction 1 of Table E the transformation of a nitrile into an amidine by the Pinner methodology is shown; in reaction 2 the direct reduction of a nitrile by a hydride reducing agent to a methylene amine is illustrated. In reaction 3, the utility of a carboxylic acid, which may be readily derived from its ester or a nitrile if necessary, in the preparation of a methylene amine is shown. This synthetic route is exceptionally flexible because of the

several stable intermediates prepared en route to the final product. As outlined, formation of an activated analog, such as the mixed anhydride, allows for the mild reduction of the acid to the methylene alcohol, this may in turn be transformed into a leaving group by sulfonylation or halogenation or protected with a suitable protecting group to be transformed later in the synthesis as the chemistry demands. Once the methylene alcohol is so activated, displacement by an efficient nitrogen nucleophile, such as azide anion, can again provide another suitably stable analog, -the methylene azide- which may be used as a protected form of the methylene amine or transformed directly into the methylene amine group by reduction. Reaction 4 addresses the problem of appending the amine functionality directly through a bond to group E of Formula 1. Once again, the carboxylic acid provides a convenient entre into this selection for group D. The well-know Curtius rearrangement is illustrated here; an activated acid analog can be used to form an acyl azide which upon thermal decomposition is rearranged to the corresponding isocyanate. The isocyanate intermediate may then be captured as a stable carbamate by the addition of a suitable alcohol and further heating. This carbamate can be used as a stable protecting group for the amine or cleaved directly to the desired D. Alternatively, it may be convenient to quench the isocyanate intermediate with water to give the amine directly.

Other features of the invention will become apparent in the course of the following descriptions of exemplary embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

EXAMPLES

Example 1

3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide, trifluoroacetic acid salt

Part A: 2-Carboxy-4-methoxyphenylhydrazine: 2-Nitro-5-methoxybenzoic acid (5.0 g) in methanol (150 mL) was shaken

under an atmosphere of hydrogen (50 psi) in the presence of 10% palladium on carbon catalyst (0.5 g) until hydrogen uptake ceased (ca. 3 h). The methanol solution was purge with nitrogen, filtered through a pad of Celite® and evaporated.

5 There was obtained 4.2 g (25.1 mmol) of the aniline; ESI mass spectrum analysis m/z (relative intensity) 168 (M+H, 100).

The aniline prepared above (4.2 g, 25.1 mmol) in concentrated hydrochloric acid (50 mL) was cooled to 0°C and sodium nitrite (2.08 g, 30.2 mmol) in cold water (20 mL) was added dropwise. This mixture was stirred at 0°C for 30 min -
10 1 h then tin(II)chloride dihydrate (17.0 g, 75.4 mmol) in cold concentrated hydrochloric acid (25 mL) was added dropwise. This mixture was allowed to thaw to ambient temperature over 3-5 h then filtered and air dried for several more. The
15 filter cake was broken up and dried further in a vacuum oven at 60°C overnight. There was obtained 8.76 g of 2-carboxy-4-methoxyphenylhydrazine tin salt.

Part B: Ethyl 2-N-(methoxy)imino-4-oxopentanoate: A mixture
20 of ethyl pentanoate-2,4-dione (24.5 g, 154.9 mmol) and methoxyamine hydrogen chloride (13.58 g, 162.6 mmol) in ethanol (100 mL) was allowed to stand over activated 3 Å molecular sieves (75 g) at ambient temperature for 18h. Following removal of the molecular sieves by filtration,
25 dichloromethane (100 mL) was added and the reaction filtered. The resulting solution was evaporated and the residue applied to a silica gel column. The title compound was isolated in a homogenous form by elution with 5:1 hexane:ethyl acetate to give 9.09 g of product.

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Part C: Ethyl 3-methyl-1-(2-carboxy-4-methoxyphenyl)-1H-pyrazole-5-carboxylate and ethyl 5-methyl-1-(2-carboxy-4-methoxyphenyl)-1H-pyrazole-3-carboxylate: Ethyl 2-N-(methoxy)imino-4-oxopentanoate (1.0 g, 5.35 mmol) and crude 2-
35 carboxy-4-methoxyphenylhydrazine (5.83 g) in acetonitrile (40 mL) and acetic acid (5 mL) was stirred at ambient temperature for 3 h then heated at reflux for an additional 3 h. The reaction was cooled to ambient temperature, diluted with

methylene chloride (150 mL) and filtered. The filtrate was evaporated and the product isolated by flash chromatography by elution with 10% methanol in chloroform. This material (1.28 g) co-eluted as a mixture of regioisomers as evident by proton NMR. ESI mass spectrum analysis m/z (relative intensity) 306 (M+H, 100).

Part D: Ethyl 3-methyl-1-(2-hydroxymethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylate and ethyl 5-methyl-1-(2-hydroxymethyl-4-methoxyphenyl)-1H-pyrazole-3-carboxylate: The mixture of regioisomers prepared in part C (1.28 g, 4.2 mmol) was dissolved in tetrahydrofuran (60 mL) and cooled to 0°C. To the cold solution was added N-methylmorpholine (0.42 g, 4.2 mmol) and isobutylchloroformate (0.57 g, 4.2 mmol). The reaction was stirred for 30 min at 0°C, the precipitate removed by filtration and the cold solution poured immediately into a cold (5°C) solution of sodium borohydride (0.48 g, 12.6 mmol) in water (20 mL) and tetrahydrofuran (20 mL). The reaction was allowed to thaw to room temperature over 18 h. The reaction mixture was evaporated, partitioned between ethyl acetate (100 mL) and 1N hydrochloric acid (50 mL), then washed with 5% sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried and evaporated; three products were isolated by elution of the crude mixture from a silica gel column with 2:1 hexane:ethyl acetate. The first product to elute was a ring closed lactone (0.14 g); ESI mass spectrum analysis m/z (relative intensity) 245 (M+H, 100). The second product isolated was ethyl 3-methyl-1-(2-hydroxymethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylate (0.18 g) as determined by proton NMR nOe experiments; ESI mass spectrum analysis m/z (relative intensity) 291 (M+H, 100). The third product to elute was the regioisomer ethyl 5-methyl-1-(2-hydroxymethyl-4-methoxyphenyl)-1H-pyrazole-3-carboxylate (0.14 g); ESI mass spectrum analysis m/z (relative intensity) 291 (M+H, 100).

Part E: Ethyl 3-methyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylate: Ethyl 3-methyl-1-(2-hydroxymethyl-4-

methoxyphenyl)-1H-pyrazole-5-carboxylate (0.18 g, 0.62 mmol) was dissolved in chloroform (20 mL) then methanesulfonyl chloride (0.3 g, 2.6 mmol) and triethylamine (0.26 g, 2.6 mmol) added. The reaction was complete in 6 h; it was
5 evaporated, dissolved in ethyl acetate (100 mL), washed with 1N hydrochloric acid (50 mL) and brine (50 mL), dried and evaporated to give 0.22 g of product.

The mesylate prepared above (0.22 g, 0.6 mmol) and sodium azide (0.12 g, 1.79 mmol) were dissolved in dimethylformamide
10 (15 mL) and heated for 1.5 h at 60°C, then diluted with brine (50 mL), extracted with ethyl acetate (100 mL), dried and evaporated. There was obtained 0.11 g of ethyl 3-methyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylate; ESI mass spectrum analysis m/z (relative intensity) 316 (M+H,
15 100).

Part F: 3-Methyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid: Ethyl 3-methyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylate (0.11 g, 0.35 mmol)
20 in ethanol (2 mL) and water (2 mL) was stirred with 50% sodium hydroxide (3 drops) at 45°C and followed by TLC (1:1 hexane:ethyl acetate). When all of the ester was consumed the reaction was cooled, diluted with brine and washed with ethyl ether (25 mL). The aqueous layer was acidified with 1N
25 hydrochloric acid (pH = 1), extracted with ethyl acetate (2x 30 mL), dried and evaporated. There was obtained 3-methyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid (0.06 g); ESI mass spectrum analysis m/z (relative intensity) 285 (M+H, 100).

30 Part G: 3-Methyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(2-N-t-butylsulfamido)phenyl)phenyl)carboxamide: 3-Methyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid
35 (0.60 g, 0.21 mmol) in dichloromethane (5 mL) was cooled to 0°C and oxalyl chloride (0.21 mL of a 2M solution in dichloromethane) and dimethyl formamide (1 drop) were added. The reaction was complete inside of 1 h; it was evaporated and

pumped on to remove residual HCl. There was obtained 0.17 g of the acid chloride.

To the acid chloride prepared above (0.17 g, 0.50 mmol) in dichloromethane (3 mL) was added dropwise to an ice-cold solution of 4-(2-N-tertbutylsulfonamido)phenyl aniline (0.15 g, 0.51 mmol), pyridine (0.39 g, 4.4 mmol) and 4,4-dimethylaminopyridine (0.09 g, 0.7 mmol) in dichloromethane (15 mL). The reaction was allowed to warm to ambient temperature over 18 h, then evaporated, dissolved in ethyl acetate (30 mL), washed with 1N hydrochloric acid (20 mL) and dried. Silica gel flash chromatography, eluting with a gradient of 2:1 to 1:1 hexane:ethyl acetate, gave 0.09 g of 3-methyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(2-N-t-butylsulfamido)phenyl)phenyl)carboxamide; ESI mass spectrum analysis m/z (relative intensity) 572 (M+H, 100).

Part H: 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide•TFA: 3-Methyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-N-t-butylsulfamido-[1,1']-biphen-4-yl))carboxamide (0.09 g, 0.16 mmol) was stirred with tin(II) chloride dihydrate (0.11 g, 0.47 mmol) in methanol (10 mL). When the reaction was complete by TLC (1:1 hexane:ethyl acetate) it was evaporated to give a crude mixture of the aminomethyl product and tin salts weighing 0.39 g. The material was heated at reflux in trifluoroacetic acid (10 mL) for 45 min then evaporated. The residue was partitioned between 1N sodium hydroxide (30 mL) and ethyl acetate (30 mL). The ethyl acetate solution was dried and evaporated to give 0.04 g of crude product. This material was purified further by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give 0.010 g of the title compound; mp 184.3°C; HRMS (M+H)⁺ calc. m/z: 492.170551, obs m/z: 492.171712.

Example 2

5-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-3-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide, trifluoroacetic acid salt

5 The regioisomeric acid prepared in Example 1, ethyl 5-methyl-1-(2-hydroxymethyl-4-methoxyphenyl)-1H-pyrazole-3-carboxylate (0.14 g, 0.48 mmol), was transformed into the azidomethyl analog, coupled with 4-(2-N-tertbutylsulfonamido)phenyl aniline and transformed into 5-methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-3-(N-(4-(2-sulfamido)phenyl)phenyl)carboxamide by the same procedures described in Example 1. The final product was purified further by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column; HRMS (M+H)⁺ calc. m/z: 492.170551, obs m/z: 492.169327.

Example 3

3-methyl-1-(2-N,N-dimethylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-N-methylsulfamido-[1,1']-biphen-4-yl))carboxamide, trifluoroacetic acid salt

3-Methyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-N-t-butylsulfamido-[1,1']-biphen-4-yl))carboxamide (0.09 g, 0.16 mmol), prepared in Example 1, was stirred with tin(II) chloride dihydrate (0.11 g, 0.47 mmol) in methanol (10 mL). When the reaction was complete by TLC (1:1 hexane:ethyl acetate) it was evaporated to give a crude mixture of the aminomethyl product and tin salts weighing 0.39 g. A portion of the crude reduction product (0.1 g, 0.20 mmol) prepared above was stirred at ambient temperature with methyl iodide (0.2 mL), and potassium hydrogen carbonate (solid, 0.2 g) in methanol (4 mL) at ambient temperature. After 18 h the reaction was evaporated and stirred with chloroform (30 mL), filtered and evaporated again to give 0.28 g of crude product.

The material from above was heated at reflux in trifluoroacetic acid (10 mL) for 45 min then evaporated. The residue was partitioned between 1N sodium hydroxide (30 mL)

and ethyl acetate (30 mL). The ethyl acetate solution was dried and evaporated to give crude product. This material was purified further by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give the title compound; mp 114.5°C; HRMS (M+H)⁺ calc. m/z: 534.217502, obs m/z: 534.218000.

Example 4

10 **3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1]-biphen-4-yl))carboxamide, trifluoroacetic acid salt**

Part A: 3-Trifluoromethyl-1-(2-carboxy-4-methoxyphenyl)-5-(furan-2-yl)-1H-pyrazole: Crude 2-carboxy-4-methoxyphenylhydrazine (8.88 g), prepared in Example 1, and 4,4,4-trifluoro-1-(2-furyl)-1,3-butanedione (7.4 g, 135.9 mmol) in acetic acid (150 mL) was heated at 100°C for 4 h. The hot reaction mixture was evaporated and the residue stirred in a biphasic mixture of water (150 mL) and chloroform (150 mL). The layers were filtered and separated, the solid precipitate washed several times with additional chloroform (3x 50 mL) and the chloroform layer and washings combined, dried and evaporated. There was obtained 3.55 g of 3-trifluoromethyl-1-(2-carboxy-4-methoxyphenyl)-5-(furan-2-yl)-1H-pyrazole; ESI (-ve) mass spectrum analysis m/z (relative intensity) 351 (M-H, 100).

Part B: 3-Trifluoromethyl-1-(2-hydroxymethyl-4-methoxyphenyl)-5-(furan-2-yl)-1H-pyrazole: 3-Trifluoromethyl-1-(2-carboxy-4-methoxyphenyl)-5-(furan-2-yl)-1H-pyrazole (3.55 g, 10.1 mmol) in tetrahydrofuran (100 mL) was cooled to 0°C then N-methylmorpholine (1.02 g, 10.1 mmol) and isobutyl chloroformate (1.38 g, 10.1 mmol) were added. The reaction mixture was stirred for 30 min at 0°C, filtered and added immediately to a cold solution of sodium borohydride (1.15 g, 30.2 mmol) in water (50 mL) and tetrahydrofuran (50 mL). The reaction mixture was evaporated, partitioned between ethyl

acetate (100 mL) and 1N hydrochloric acid (50 mL), then washed with 5% sodium bicarbonate (50 mL) and brine (50 mL). The organic layer was dried and evaporated then purified further by flash chromatography using 4:1 hexane:ethyl acetate as the eluent. There was obtained 1.5 g of 3-trifluoromethyl-1-(2-hydroxymethyl-4-methoxyphenyl)-5-(furan-2-yl)-1H-pyrazole; ESI mass spectrum analysis m/z (relative intensity) 339 (M+H, 100).

10 Part C: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-5-(furan-2-yl)-1H-pyrazole: To a cooled chloroform (50 mL) solution of 3-trifluoromethyl-1-(2-hydroxymethyl-4-methoxyphenyl)-5-(furan-2-yl)-1H-pyrazole (1.5 g, 4.44 mmol) and triethylamine (1.79 g, 17.7 mmol) was added a chloroform
15 solution (10 mL) of methanesulfonyl chloride (2.03 g, 17.7 mmol). The reaction was complete in 4 h. It was evaporated, dissolved in ethyl acetate (100 mL) and the ethyl acetate solution washed with cold 5% NaHSO₄ (50 mL) and cold saturated NaHCO₃ (50 mL). The organic layer was dried and evaporated to
20 give 2.1 g of the mesylate which was used immediately in the next reaction; ESI mass spectrum analysis m/z (relative intensity) 417(M+H, 100).

A mixture of the mesylate prepared above (2.1 g, 5.05 mmol) and sodium azide (0.98 g, 15.1 mmol) in
25 dimethylformamide (40 mL) was heated at 60°C for 2 h. The reaction mixture was cooled, diluted with brine (100 mL) and extracted with ethyl acetate (100 mL). The ethyl acetate extract was washed with water (5x 50 mL) then dried and evaporated. There was obtained 1.43 g of 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-5-(furan-2-yl)-1H-pyrazole; ESI mass spectrum analysis m/z (relative intensity) 364 (M+H, 100).

35 Part D: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid: To 1.43 g of 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-5-(furan-2-yl)-1H-pyrazole (3.9 mmol) in acetone (60 mL) was added potassium permanganate (5.0 g, 27.5 mmol) in water (60 mL).

The reaction was heated at 60°C for 3 h, then cooled to ambient temperature and isopropyl alcohol (60 mL) added. This mixture was stirred for 18 h then filtered through a Celite® pad and washed with copious amounts of isopropyl alcohol. The combined filtrates were evaporated, the residue dissolved in 1N NaOH (50 mL) and washed with ethyl ether (2x 50 mL). The basic layer was acidified with 1N HCl (75 mL) and solid NaCl added. The suspension was extracted with EtOAc (3x 100 mL); the extracts were dried and evaporated. There was obtained 0.91 g of 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid; ESI (-ve) mass spectrum analysis m/z (relative intensity) 340 (M-H, 100).

Part E: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid chloride: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid (1.09 g, 3.2 mmol) in dichloromethane (50 mL) was stirred at 0°C with oxalyl chloride from 3.2 mL of a 2M dichloromethane solution of the reagent and a catalytic amount of DMF (3 drops). The reaction was complete in 3 h, then evaporated and pumped on to remove residual reagent. There was obtained 1.04 g (2.9 mmol) of 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid chloride.

Part F: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-(2-N-tertbutylsulfamido-[1,1]-biphen-4-yl))carboxamide: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid chloride prepared above (0.52 g, 1.45 mmol) in dichloromethane (10 mL) was added dropwise to an ice-cold solution of 2-fluoro-4-(2-N-tertbutylsulfonamido)phenyl aniline (0.56 g, 1.74 mmol), pyridine (1.14 g, 14.5 mmol) and 4,4-dimethylaminopyridine (0.21 g, 1.74 mmol) in dichloromethane (30 mL). The reaction was allowed to warm to ambient temperature over 18 h, then evaporated, dissolved in ethyl acetate (100 mL), washed with 1N hydrochloric acid (50 mL) and dried. Silica gel flash chromatography, eluting with 4:1 hexane:ethyl acetate, gave 0.28 g of 3-trifluoromethyl-1-(2-

azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-(2-N-tertbutylsulfamidophenyl)phenyl)carboxamide; ESI (-ve) mass spectrum analysis m/z (relative intensity) 644 (M-H, 100).

5 Part G: 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphen-1-yl)-1H-pyrazole-5-(N-(2-fluoro-4-(2-sulfamido-[1,1]-biphen-4-yl))carboxamide•TFA: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-(2-N-tertbutylsulfamidophenyl)phenyl)carboxamide (0.28 g, 0.43
10 mmol) and tin(II)chloride dihydrate (0.29 g, 1.3 mmol) was stirred in methanol (30 mL) for 18 h. The reaction was evaporated and the reduction product (0.60 g) was carried on to the next step without further processing.

The product prepared above was refluxed in
15 trifluoroacetic acid (20 mL) for 30 min, then evaporated. The residue was suspended in 1N NaOH (30 mL), extracted with EtOAc (3x 50 mL), dried and evaporated. This material was purified further by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a
20 reverse phase C18 (60 Å) column to give the title compound; mp 103.2 °C; ESI mass spectrum analysis m/z (relative intensity) 564.2 (M+H, 100).

Example 5

25 **3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide, trifluoroacetic acid salt**

Part A: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-
30 1H-pyrazole-5-(N-(2-fluoro-4-(2-methylsulfonylphenyl)phenyl)carboxamide: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid chloride prepared in Example 4 (0.52 g, 1.45 mmol) in dichloromethane (10 mL) was added dropwise to an ice-cold
35 solution of 2-fluoro-4-(2-methylsulfonylphenyl)aniline (0.52 g, 1.74 mmol), pyridine (1.14 g, 14.5 mmol) and 4,4-dimethylaminopyridine (0.21 g, 1.74 mmol) in dichloromethane (30 mL). The reaction was allowed to warm to ambient

temperature over 18 h, then evaporated, dissolved in ethyl acetate (100 mL), washed with 1N hydrochloric acid (50 mL) and dried. Silica gel flash chromatography, eluting with a gradient of 5:1 to 1:1 hexane:ethyl acetate, gave 0.46 g of 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-(2-methylsulfonylphenyl)phenyl)carboxamide; ESI mass spectrum analysis m/z (relative intensity) 587(M+H, 100).

Part B: 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide•TFA: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide (0.46 g, 0.78 mmol) and tin(II)chloride dihydrate (0.53 g, 2.35 mmol) was stirred in methanol (25 mL) for 18 h. The reaction was evaporated and the residue was suspended in 1N NaOH (50 mL), extracted with EtOAc (3x 100 mL), dried and evaporated to give 0.29 g of crude product. This material was purified further by hplc utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give the title compound; mp 101.5 °C; ESI mass spectrum analysis m/z (relative intensity) 563(M+H, 100).

25

Example 6

3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide, trifluoroacetic acid salt

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Part A: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid chloride and 4-(2-methylsulfonylphenyl)aniline were treated in the manner described for Example 5, Part A to give 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(2-methylsulfonylphenyl)phenyl)carboxamide.

Part B: 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1]-biphen-4-yl))carboxyamide•TFA: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(2-methylsulfonylphenyl)phenyl)carboxyamide was treated in the same manner as Example 5, Part B to give the title compound; HRMS (M+H)⁺ calc. m/z: 545.147037, obs m/z: 545.145700.

10

Example 7

3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1]-biphen-4-yl))carboxyamide, trifluoroacetic acid salt

15 Part A: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-N-tertbutylsulfamido-[1,1]-biphen-4-yl))carboxyamide: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid chloride and 4-(2-N-tertbutylsulfonamido)phenyl aniline were treated as described in Example 4, Part F to give 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(2-N-tertbutylsulfamidophenyl)phenyl)carboxyamide.

25 Part B: 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1]-biphen-4-yl))carboxyamide•TFA: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-(2-N-tertbutylsulfamidophenyl)phenyl)carboxyamide was treated as described in Example 4, Part G to give the title compound; LRMS (M+H)⁺: m/z 546.2.

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Example 8

3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-pyrrolidinocarbonyl)phenyl)carboxyamide•TFA

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Part A: 5-(Furan-2-yl)-3-trifluoromethyl-1-(2-carboxyl-4-methoxyphenyl)-1H-pyrazole: 3-Methoxy-6-aminobenzoic acid (23

g, 138 mmol) in conc. HCl (300 mL) was cooled to 0 °C and NaNO₂ (11.4 g, 165 mmol) in H₂O (50 mL) was added dropwise while the temperature of the reaction was maintained below 10 °C. The reaction was stirred at or below 10 °C for 1 h, then SnCl₂·H₂O (92.3 g, 413 mmol) in conc. HCl (125 mL) was added dropwise. The reaction was allowed to thaw to ambient temperature and stirred for 3 h. The precipitate was filtered and air-dried then heated in a vacuum oven for 18 h. There was obtained 71.4 g of 3-methoxy-6-hydrazinobenzoic acid entrained with tin (II) salts.

The hydrazine prepared above (71.4 g) in acetic acid (800 mL) was heated at 45 °C until dissolved, then 4,4,4-trifluoromethyl-1-(2-furyl)-1,3-butanedione (28.42 g, 138 mmol) was added and the mixture heated at reflux for 2.5 h. The reaction was cooled and evaporated to dryness. The residue was partitioned between H₂O (400 mL) and CHCl₃ (400 mL) and stirred for 30 min. The biphasic mixture was filtered, the layers separated and the organic layer dried (Na₂SO₄) and evaporated to give 49.4 g of 5-(furan-2-yl)-3-trifluoromethyl-1-(2-carboxyl-4-methoxyphenyl)-1H-pyrazole; LRMS (ES⁻) M⁻: 351 m/z.

Part B: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid: To a solution of 5-(furan-2-yl)-3-trifluoromethyl-1-(2-carboxyl-4-methoxyphenyl)-1H-pyrazole (49.4 g, 140.3 mmol) in THF (600 mL) at 0 °C was added N-methylmorpholine (14.9 g, 147 mmol) and isobutylchloroformate (20.1 g, 147.3 mmol). After 3 h at 0 °C, the reaction mixture was filtered into a H₂O:THF (200 mL: 200 mL) solution of NaBH₄ (10.6 g, 280 mmol) at 0 °C. After 18 h, the reaction was quenched with 1N HCl (500 mL) then the THF was removed in vacuo. The remaining aqueous suspension was saturated with solid NaCl and extracted with EtOAc, dried (Na₂SO₄) and evaporated. The crude product was recrystallized from 1-chlorobutane to give 16.8 g of benzyl alcohol product. The mother liquors were applied to a column of flash SiO₂ (500

g) and eluted with 2:1 hexane: EtOAc to give 8.7 g of benzyl alcohol product; LRMS ES⁺ (M+H)⁺: 339 m/z.

5 The benzyl alcohol product (8.7 g, 25.1 mmol) prepared above and Et₃N (3.1 g, 30.9 mmol) in CH₂Cl₂ (200 mL) was cooled to 0 °C. Methanesulfonyl chloride (3.5 g, 30.9 mmol) in CH₂Cl₂ (10 mL) was added dropwise. The cooling bath was removed and the reaction stirred for 3 h. A 5% solution of NaHSO₄ (200 mL) was added, the organic layer was separated, dried and evaporated
10 to give 10.25 g of mesylate.

The mesylate (10.25 g, 24.6 mmol) from above and NaN₃ (4.8 g, 73.8 mmol) in DMF (100 mL) was stirred at ambient temperature for 18 h. The reaction was diluted with brine (500 mL),
15 extracted with EtOAc and the extracts washed with H₂O (5 x 150 mL). The EtOAc layer was dried (Na₂SO₄) and evaporated to give 8.16 g of the azidomethyl compound; LRMS ES⁺ (M+H)⁺: 364 m/z.

The azidomethyl compound (23 g, 63.4 mmol) in acetone (400 mL) was heated at 60 °C, then KMnO₄ (50 g, 317 mmol) in H₂O (300 mL) was added. After addition was complete, the reaction was heated for 1.5 h. The cooled reaction was filtered through a pad of Celite® and evaporated. The water layer was made basic with 1N NaOH (200 mL) and washed with Et₂O (3x),
25 then acidified with conc. HCl, saturated with solid NaCl and extracted with EtOAc (3x). The EtOAc layer was dried and evaporated to give 15.1 g of 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid; LRMS ES⁻ (M-H)⁻: 340 m/z.

30

Part C: 3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-carboxylpyrrolidino)phenyl)carboxamide: To 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid (0.44 g, 1.29 mmol) prepared above
35 in CH₂Cl₂ at 0 °C was added a 2M solution of oxalyl chloride in CH₂Cl₂ (2 equivalents, 1.29 mL) followed by a drop of DMF. The ice bath was removed and the reaction stirred for 3 h then evaporated. The resulting acid chloride was combined with N-

(4-aminobenzoyl)pyrrolidine (0.32 g, 1.68 mmol) and DMAP (0.47 g, 3.87 mmol) and dissolved in CH_2Cl_2 (20 mL). The reaction was stirred for 18 h, then evaporated and dissolved in EtOAc. The EtOAc layer was washed with 1N HCl and brine, dried
5 (Na₂SO₄) and evaporated. The product was purified further by a column of flash SiO₂ (50 g) eluting with 5-10 % MeOH in CHCl_3 to give 0.24 g of 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-carboxylpyrrolidino)phenyl)carboxamide; LRMS ES⁺ (M+H)⁺: 514
10 m/z.

Part D: 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-carboxylpyrrolidino)phenyl)carboxamide•TFA: A mixture of 3-
15 trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-carboxylpyrrolidino)phenyl)carboxamide (0.24 g, 0.27 mmol) and $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (0.24 g, 0.95 mmol) in MeOH (20 mL) was stirred for 18 h. The reaction was evaporated and dissolved in 1N NaOH. The basic layer was extracted with
20 EtOAc dried and evaporated. The crude product was purified further by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give 31.2 mg of title compound; mp 117.5 °C; HRMS (M+H)⁺ calc. m/z: 488.190950,
25 obs: 488.191005.

Example 9

N-Benzylsulfonyl-4-(3-trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxamido)piperidine•TFA
30

3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid prepared in Part B of Example 8 was coupled with N-Benzylsulfonyl-4-aminopiperidine according to
35 the procedure in Part C of Example 8. The title compound was prepared and purified by the method outlined in Part D of Example 8; mp 98.3 °C; HRMS (M+H)⁺ calc. m/z: 552.189236 obs: 552.188800.

Example 10

3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2'-sulfonamido)phenyl)pyrid-2-yl)carboxamide•TFA

3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid prepared in Part B of Example 8 was coupled with 2-amino-5-((2-N-t-butylsulfonamido)phenyl)pyridine according to the procedure in Part C of Example 8. The azidomethyl group was reduced to the aminomethyl group with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ by the method outlined in Part D of Example 8. The crude reduction product was then refluxed in trifluoroacetic acid (10 mL) for 1 h to remove the t-butyl protecting group. The title compound was isolated by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column; mp 86.6 °C; HRMS (M+H)⁺ calc. m/z: 547.137535, obs: 547.138200.

Example 11

3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(pyrid-2-yl))pyrid-2-yl)carboxamide•TFA

3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid prepared in Part B of Example 8 was coupled with 2-amino-5-(pyrid-2-yl)pyridine according to the procedure in Part C of Example 8. The title compound was prepared and purified by the method outlined in Part D of Example 8; mp 48.2 °C; HRMS (M+H)⁺: 469.1602 m/z.

Example 12

N-Benzyl-4-(3-trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxamido)piperidine•TFA

3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid prepared in Part B of Example 8 was coupled with N-Benzyl-4-aminopiperidine according to the procedure in Part C of Example 8. The title compound was prepared and purified by the method outlined in Part D of Example 8; mp 116.1 °C; HRMS (M+H)⁺: 488.2266 m/z.

Example 13

N-Phenylsulfonyl-4-(3-trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxyamido)piperidine•TFA

3-Trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid prepared in Part B of Example 8 was coupled with N-phenylsulfonyl-4-aminopiperidine according to the procedure in Part C of Example 8. The title compound was prepared and purified by the method outlined in Part D of Example 8; mp 103 °C; HRMS (M+H)⁺: 538.1729 m/z.

20

Example 14

3-Trifluoromethyl-1-(2-aminomethyl-4-chlorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide•TFA

3-Trifluoromethyl-1-(2-azidomethyl-4-chlorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 3-chloro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This compound was coupled with 2-fluoro-4-((2-methansulfonyl)phenyl)aniline according to the procedure in Part C of Example 8. The title compound was prepared and purified by the method outlined in Part D of Example 8; mp 97.5 °C; HRMS (M+H)⁺: 567.0891 m/z.

35

Example 15

3-Trifluoromethyl-1-(2-aminomethyl-4-chlorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide•TFA

5 3-Trifluoromethyl-1-(2-azidomethyl-4-chlorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 3-chloro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This
10 compound was coupled with 2-fluoro-4-((2-N-t-butylsulfonamido)phenyl)aniline according to the procedure in Part C of Example 8. The azidomethyl group was reduced to the aminomethyl group with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ by the method outlined in Part D of Example 8. The crude reduction product was then
15 refluxed in trifluoroacetic acid (10 mL) for 1 h to remove the t-butyl protecting group. The title compound was isolated by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column; mp 128 °C; HRMS (M+H)⁺:
20 568.0832 m/z.

Example 16

3-Trifluoromethyl-1-(2-aminomethyl-5-chlorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methanesulfonyl-[1,1']-biphen-4-yl))carboxamide•TFA

25

3-Trifluoromethyl-1-(2-azidomethyl-5-chlorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 4-chloro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This
30 compound was coupled with 2-fluoro-4-((2-methanesulfonyl)phenyl)aniline according to the procedure in Part C of Example 8. The title compound was prepared and
35 purified by the method outlined in Part D of Example 8; mp 99.7 °C; HRMS (M+H)⁺: 567.0859 m/z.

Example 17

3-Trifluoromethyl-1-(2-aminomethyl-4-chlorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide•TFA

5 3-Trifluoromethyl-1-(2-azidomethyl-5-chlorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 4-chloro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This
10 compound was coupled with 2-fluoro-4-((2-N-t-butylsulfonamido)phenyl)aniline according to the procedure in Part C of Example 8. The azidomethyl group was reduced to the aminomethyl group with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ by the method outlined in Part D of Example 8. The crude reduction product was then
15 refluxed in trifluoroacetic acid (10 mL) for 1 h to remove the t-butyl protecting group. The title compound was isolated by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column; mp 127.4 °C; HRMS (M+H)⁺:
20 568.0837 m/z.

Example 18

3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide•TFA

25

3-Trifluoromethyl-1-(2-azidomethyl-4-fluorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 3-fluoro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This
30 compound was coupled with 2-fluoro-4-((2-methansulfonyl)phenyl)aniline according to the procedure in Part C of Example 8. The title compound was prepared and
35 purified by the method outlined in Part D of Example 8; mp 125 °C; HRMS (M+H)⁺: 551.1177 m/z.

Example 19

3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide•TFA

5 3-Trifluoromethyl-1-(2-azidomethyl-4-fluorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 3-fluoro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This
10 compound was coupled with 2-fluoro-4-((2-N-t-butylsulfonamido)phenyl)aniline according to the procedure in Part C of Example 8. The azidomethyl group was reduced to the aminomethyl group with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ by the method outlined in Part D of Example 8. The crude reduction product was then
15 refluxed in trifluoroacetic acid (10 mL) for 1 h to remove the t-butyl protecting group. The title compound was isolated by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column; mp 113.1 °C; HRMS (M+H)⁺:
20 552.1112 m/z.

Example 20

3-Trifluoromethyl-1-(2-aminomethyl-5-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methanesulfonyl-[1,1']-biphen-4-yl))carboxamide•TFA

25

3-Trifluoromethyl-1-(2-azidomethyl-5-fluorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 4-fluoro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This
30 compound was coupled with 2-fluoro-4-((2-methanesulfonyl)phenyl)aniline according to the procedure in Part C of Example 8. The title compound was prepared and
35 purified by the method outlined in Part D of Example 8; mp 97.2 °C; HRMS (M+H)⁺: 551.1179 m/z.

Example 21

3-Trifluoromethyl-1-(2-aminomethyl-5-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide•TFA

5 3-Trifluoromethyl-1-(2-azidomethyl-5-fluorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 4-fluoro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This
10 compound was coupled with 2-fluoro-4-((2-N-t-butylsulfonamido)phenyl)aniline according to the procedure in Part C of Example 8. The azidomethyl group was reduced to the aminomethyl group with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ by the method outlined in Part D of Example 8. The crude reduction product was then
15 refluxed in trifluoroacetic acid (10 mL) for 1 h to remove the t-butyl protecting group. The title compound was isolated by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column; mp 101 °C; HRMS (M+H)⁺:
20 552.1120 m/z.

Example 22

3-Trifluoromethyl-1-(2-aminomethyl-4,5-difluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide•TFA

25

3-Trifluoromethyl-1-(2-azidomethyl-4,5-difluorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 3,4-difluoro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This
30 compound was coupled with 2-fluoro-4-((2-methansulfonyl)phenyl)aniline according to the procedure in Part C of Example 8. The title compound was prepared and
35 purified by the method outlined in Part D of Example 8; HRMS (M+H)⁺: 569.1082 m/z.

Example 21

3-Trifluoromethyl-1-(2-aminomethyl-4,5-difluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide•TFA

5 3-Trifluoromethyl-1-(2-azidomethyl-4,5-difluorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 3,4-difluoro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This
10 compound was coupled with 2-fluoro-4-((2-N-t-butylsulfonamido)phenyl)aniline according to the procedure in Part C of Example 8. The azidomethyl group was reduced to the aminomethyl group with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ by the method outlined in Part D of Example 8. The crude reduction product was then
15 refluxed in trifluoroacetic acid (10 mL) for 1 h to remove the t-butyl protecting group. The title compound was isolated by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column; mp 118.7 °C; HRMS (M+H)⁺:
20 570.1038 m/z.

Example 24

3-Trifluoromethyl-1-(2-aminomethyl-3-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide•TFA

25

3-Trifluoromethyl-1-(2-azidomethyl-3-fluorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 2-fluoro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This
30 compound was coupled with 2-fluoro-4-((2-methansulfonyl)phenyl)aniline according to the procedure in Part C of Example 8. The title compound was prepared and
35 purified by the method outlined in Part D of Example 8; mp 105.1 °C; HRMS (M+H)⁺: 551.1180 m/z.

Example 25

3-Trifluoromethyl-1-(2-aminomethyl-3-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide•TFA

5 3-Trifluoromethyl-1-(2-azidomethyl-3-fluorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 2-fluoro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This
10 compound was coupled with 2-fluoro-4-((2-N-t-butylsulfonamido)phenyl)aniline according to the procedure in Part C of Example 8. The azidomethyl group was reduced to the aminomethyl group with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ by the method outlined in Part D of Example 8. The crude reduction product was then
15 refluxed in trifluoroacetic acid (10 mL) for 1 h to remove the t-butyl protecting group. The title compound was isolated by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column; mp 115.8 °C; HRMS (M+H)⁺:
20 552.1111 m/z.

Example 26

3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(4-(2-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide•TFA

25

3-Trifluoromethyl-1-(2-azidomethyl-4-fluorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 3-fluoro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This
30 compound was coupled with 4-((2-methansulfonyl)phenyl)aniline according to the procedure in Part C of Example 8. The title compound was prepared and purified by the method outlined in
35 Part D of Example 8; mp 110.3 °C; HRMS (M+H)⁺: 533.1265 m/z.

Example 27

3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(4-(2-sulfamido-[1,1']-biphen-4-yl))carboxamide•TFA

5 3-Trifluoromethyl-1-(2-azidomethyl-4-fluorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 3-fluoro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This
10 compound was coupled with 4-((2-N-t-butylsulfonamido)phenyl)aniline according to the procedure in Part C of Example 8. The azidomethyl group was reduced to the aminomethyl group with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ by the method outlined in Part D of Example 8. The crude reduction product was then
15 refluxed in trifluoroacetic acid (10 mL) for 1 h to remove the t-butyl protecting group. The title compound was isolated by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column; mp 136.8 °C; HRMS (M+H)⁺:
20 534.1227 m/z.

Example 28

3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(4-(N-(N'-methanolsulfonyl)iminol)pyrrolidino))phenyl)carboxamide•TFA

Part A: 4-Amino-N-((N'-methanolsulfonyl)iminol)pyrrolidine :
4-Nitrobenzonitrile (5.4 g, 36.5 mmol) in anhydrous methyl acetate (200 mL) and MeOH (20 mL) was cooled to 0 °C and
30 treated with a stream of dry HCl gas for 1 h. The reaction was securely stoppered and left to stand at 5 °C in a refrigerator for 24 h. The solvent was removed and the reaction was evaporated repeatedly (5 x) with Et₂O to remove the last traces of free HCl. There was obtained 28.6 g of the
35 imidate as an HCl salt. This material was dissolved in anhydrous MeOH (100 mL) and pyrrolidine (40.1 mmol, 2.85 g) added. The reaction was stirred for 18 h, then evaporated and stirred in 1N HCl (150 mL); the insoluble material was

removed by filtration then the HCl solution evaporated. The residue was dried by the azeotropic removal of H₂O with EtOH and there was obtained 7.44 g of the amidine product; LRMS ES⁺ (M+H)⁺: 220.1 m/z.

5

The free base of the amidine prepared above was formed by suspending the product in 1N NaOH (250 mL) and extracting this suspension with CHCl₃ (3 x). The material was dried and evaporated to give 4.49 g of product.

10

To 3.1 g of the free base of the amidine prepared above (14.2 mmol) in CH₂Cl₂ (100 mL) at 0 °C was added DMAP (2.1 g, 17 mmol) followed by methanesulfonyl chloride (1.95 g, 17 mmol) in CH₂Cl₂ (25 mL). After 18 h at ambient temperature, the reaction was washed with 1N HCl (2 x), 1N NaOH and brine, dried and evaporated. There was obtained 3.6 g of the mesylation product; LRMS ES⁺ (M+H)⁺: 298.1.

The mesylation product (3.6 g, 12 mmol) and SnCl₂·2H₂O (8.12 g, 36 mmol) in EtOH (100 mL) was heated at reflux for 2 h. The solvent was removed and the residue partitioned between 1N NaOH (150 mL) and CH₂Cl₂ (100 mL). The aqueous layer was extracted with CH₂Cl₂ (2 x 100 mL), dried (Na₂SO₄) and evaporated to give 2.7 g of 4-amino-N-((N'-methylsulfonyl)iminoyl)pyrrolidine; LRMS ES⁺ (M+H)⁺: 268.1 m/z.

Part B: 3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(4-(N'-(N'-methylsulfonyl)iminoyl)pyrrolidino))phenyl) carboxamide·TFA: 3-Trifluoromethyl-1-(2-azidomethyl-4-fluorophenyl)-1H-pyrazole-5-carboxylic acid was prepared from 3-fluoro-6-aminobenzoic acid by essentially the same method used for 3-trifluoromethyl-1-(2-azidomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxylic acid in Parts A and B of Example 8. This compound was coupled with 4-amino-N-((N'-methylsulfonyl)iminoyl)pyrrolidine, prepared in Part A of Example 28, according to the procedure in Part C of Example 8.

The title compound was prepared and purified by the method outlined in Part D of Example 8; mp 138.4 °C; HRMS (M+H)⁺: 553.1640 m/z.

5

Example 29

3-Trifluoromethyl-1-(2-(N-glycyl)aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide•TFA

- 10 3-Trifluoromethyl-1-(2-(N-glycyl)aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide•TFA: A mixture of 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide•TFA (prepared
15 in Example 5, 0.15 g, 0.22 mmol), N-Boc glycine (0.039 g, 0.22 mmol) and HBTU (0.084 g, 0.22 mmol) in DMF (3 mL) were cooled to 0 °C and NMM (0.075 g, 0.75 mmol) added. After 6 h, the reaction was diluted with brine and extracted with EtOAc. The EtOAc layer was washed with 5% NaHSO₄ and brine (5 x) then
20 dried (MgSO₄) and evaporated to give 0.14 g of product; LRMS ES⁺ (M+H)⁺: 720.4 m/z.

- The product from above was stirred in 5% TFA in CH₂Cl₂ (20 mL) for 18 h. The reaction was evaporated and the product
25 purified by HPLC utilizing gradient elution with a mixture of water:acetonitrile with 0.05% trifluoroacetic acid on a reverse phase C18 (60 Å) column to give 0.087 g of the title compound; mp 92.5 °C; HRMS (M+H)⁺: 620.160000 m/z.

30

Example 30

3-Trifluoromethyl-1-(2-(N-phenylacetyl)aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide

- 35 3-Trifluoromethyl-1-(2-(N-phenylacetyl)aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide: A mixture of 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-

5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxyamide•TFA (prepared in Example 5, 0.15 g, 0.22 mmol) and Et₃N (0.068 g, 0.66 mmol) in CH₂Cl₂ (10 mL) was cooled to 0 °C and phenylacetyl chloride (0.22 mol in 1 mL of CH₂Cl₂) was added dropwise. The reaction was complete in 3 h. It was diluted with more CH₂Cl₂ then washed with 1N HCl, dried and evaporated. The residue was purified further by MPLC on a 200g column of flash SiO₂ by elution with 1:1 Hexane:EtOAc. Fractions (25 mL) were collected and the product isolated in tubes 44-75. There was obtained 0.086 g of the desired product; mp 179-181 °C; HRMS (M+H)⁺: 681.1786 m/z.

Example 31

3-(Trifluoromethyl)-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxyamide•TFA

2-[5-(2-Furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzoic acid: 4,4,4-Trifluoro-1-(2-furyl)-1,3-butanedione (2.4 mL, 16 mmol) was added to 2-hydrazinobenzoic acid (3.01 g, 16 mmol) in acetic acid (20 mL) and heated at reflux for 25 h. The reaction was cooled, diluted with EtOAc, and extracted twice with water. The organic layer was dried over Na₂SO₄, filtered, and evaporated to yield a thick red paste (5.71 g, >100%). ¹H NMR (CDCl₃) δ 8.18 (dd, 1H, J = 7.7, J' = 1.8), 7.74 (td, 1H, J = 7.7, J' = 1.4), 7.65 (td, 1H, J = 7.7, J' = 1.5), 7.50 (dd, 1H, J = 7.3, J' = 1.1), 7.35 (m, 1H), 6.89 (s, 1H), 6.28 (m, 1H), 5.76 (d, 1H, J = 3.3).

2-[5-(2-Furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzamide: 2-[5-(2-Furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzoic acid (5.13 g, 16 mmol) was dissolved in thionyl chloride (25 mL) and heated at reflux for 2 h. The excess thionyl chloride was evaporated, and the resulting acid chloride was placed under high vacuum. The acid chloride was then redissolved in CH₂Cl₂ (25 mL) and cooled to 0°C. Conc. aqueous NH₃ (6 mL) was added portionwise over 30 min. The resulting mixture was stirred at 0°C for 30 min, then at room temperature for 1 h.

The reaction was diluted with water and extracted with CH₂Cl₂ (3x). The organic layers were combined and extracted with 2M Na₂CO₃. The organic layer was dried over MgSO₄, filtered, and evaporated to yield the desired product (4.76 g, 93%). ¹H NMR (CDCl₃) δ 7.98 (dd, 1H, J = 7.3, J' = 2.2), 7.67 (m, 2H), 7.41 (m, 2H), 6.96 (s, 1H), 6.28 (m, 1H), 5.89 (bs, 1H), 5.67 (d, 1H, J = 2.9).

2-[5-(2-Furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzonitrile: 2-[5-(2-Furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzamide (6.73 g, 21 mmol) and triethylamine (5.8 mL, 42 mmol) were combined in dry CH₂Cl₂ (55 mL) under argon and cooled to 0°C. Trichloroacetyl chloride (2.7 mL, 24 mmol) in CH₂Cl₂ (15 mL) was added dropwise over 30 min. The resulting solution was stirred at 0°C for 20 min, then at room temperature for 65 min. The reaction was quenched with a small amount of water, then partitioned between 1M HCl and CH₂Cl₂. The organic layer was removed and extracted with sat. NaHCO₃, then dried over Na₂SO₄, filtered, and evaporated to yield crude product (6.66 g). The crude product was chromatographed on silica gel (30-40% EtOAc/hexanes) to yield a yellow solid (6.51 g, >100%). ¹H NMR (CDCl₃) δ 7.79 (m, 2H), 7.64 (m, 2H), 7.39 (d, 1H, J = 1.8), 6.96 (s, 1H), 6.37 (m, 1H), 6.04 (d, 1H, J = 3.7).

2-[5-(2-Furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzylamine: Cobalt chloride (1.76 g, 13.6 mmol) was added to 2-[5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzonitrile (4.12 g, 13.6 mmol) and sodium borohydride (1.03 g, 27.2 mmol) in DMF (40 mL). The reaction turned black and became warm. An ice bath was added and the reaction was stirred at 0°C for 45 min, then at room temperature for 23 h. Additional sodium borohydride (0.25 g, 6.6 mmol) was added and the resulting mixture was stirred at room temperature for 6 h. A room temperature water bath was added, and the reaction was quenched with water (10 mL) over 10 min, then MeOH (20 mL), then 6M HCl (20 mL) over 15 min. The quenched reaction was stirred at room temperature for 16 h, diluted with EtOAc, and

extracted with water and 0.1M HCl. The resulting emulsion was filtered through celite, and the organic layer was removed, dried over Na₂SO₄, filtered, and evaporated to yield crude product (857 mg). The aqueous layers were combined and
5 neutralized (pH 8) with solid Na₂CO₃ (6.9 g). Addition of EtOAc yielded another emulsion, which was filtered through celite. The organic layer was removed, and the aqueous layer was extracted again with EtOAc. The organic layers were combined, dried over Na₂SO₄, filtered, and evaporated to yield
10 a second batch of crude product (3.55 g). The two batches of crude product were combined and chromatographed on silica gel (0-10% MeOH/CHCl₃) to yield the desired product (3.77 g, 90%).
¹H NMR (CDCl₃) δ 7.59 (m, 2H), 7.38 (m, 2H), 7.33 (d, 1H, J = 7.3), 6.96 (s, 1H), 6.27 (m, 1H), 5.59 (d, 1H, J = 3.6), 3.51
15 (s, 2H).

t-Butyl 2-[5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzylcarbamate: Triethylamine (2.6 mL, 18.7 mmol) and di-t-butyl dicarbonate (4.0 g, 18.4 mmol) were added to 2-[5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzylamine (3.77
20 g, 12.3 mmol) in THF (60 mL) and stirred at room temperature for 17 h. The reaction was concentrated, diluted with Et₂O, and extracted with water (2x). The aqueous layers were combined and extracted with Et₂O. The organic layers were
25 combined, dried over MgSO₄, filtered, and evaporated to yield crude product (5.58 g). The crude product was chromatographed on silica gel (10-20% EtOAc/hexanes) to yield a waxy solid (3.82 g, 76%).
¹H NMR (CDCl₃) δ 7.57 (m, 2H), 7.43 (m, 2H), 7.32 (d, 1H, J = 7.7), 6.95 (s, 1H), 6.28 (m, 1H), 5.66 (d, 1H, J = 3.3), 4.82 (bs, 1H), 4.01 (bd, 2H, J = 6.2), 1.39 (s, 9H).
30

1-(2-([(t-Butoxycarbonyl)amino]methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl-5-carboxylic acid: t-Butyl
35 2-[5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzylcarbamate (3.77 g, 9.2 mmol) was dissolved in t-BuOH (60 mL). A 5% aqueous solution of NaH₂PO₄ (40 mL) was added, followed by portionwise addition of solid KMnO₄ (5.86 g, 37

mmol) over 25 min. The resulting mixture was heated at 65°C for 40 min. Additional KMnO₄ (1.39 g, 8.8 mmol) was added, and the reaction continued heating at 65°C for 35 min. The reaction mixture was cooled and filtered through celite, using EtOH and acetone to rinse the celite. The filtrate was concentrated to approx. half its original volume and treated with aq. sodium bisulfite to remove residual KMnO₄. The resulting mixture was extracted with EtOAc, and the organic layer was removed, dried over Na₂SO₄, filtered, and evaporated to yield crude product (1.50 g). The aqueous layer was cooled in ice, acidified with 1M HCl (6 mL) and extracted with EtOAc (containing a small amount of EtOH). Before separating, both layers were filtered through celite and treated with sat NaHCO₃ (1.5 mL). The aqueous layer was removed and extracted twice with EtOAc/EtOH. Solid NaCl was added both times to aid separation of the emulsion. The aqueous layer was extracted with CHCl₃, adjusted to pH 5 with 1M HCl, and extracted twice with CHCl₃/EtOH. The final 6 organic layers were combined, dried over Na₂SO₄, filtered, and evaporated to yield a second batch of product (2.43 g, 68%). The first batch of product was chromatographed on silica gel (0-30% MeOH/CHCl₃) to yield clean product (0.95 g, 27%). ¹H NMR (DMSO) δ 7.34 (m, 4H), 7.16 (d, 1H), 6.81 (bs, 1H), 3.79 (bd, 2H), 1.32 (s, 9H).

1-[2-(((t-Butoxycarbonyl)amino)methyl)phenyl)-5-(2'-methylsulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-(trifluoromethyl)pyrazole: Oxalyl chloride (90 µl, 1.0 mmol) and DMF (2 drops) were added to 1-(2-(((t-butoxycarbonyl)amino)methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl-5-carboxylic acid (200 mg, 0.52 mmol) in CH₂Cl₂ (5 mL) and the resulting solution was stirred for 90 min at room temperature. The solvents were evaporated and the resulting compound was placed briefly under high vacuum before redissolving in CH₂Cl₂ (5 mL). Triethylamine (220 µl, 1.6 mmol), 4-amino-2'-methylsulfonyl-[1,1']-biphenyl hydrochloride (177 mg, 0.62 mmol), and 4-dimethylaminopyridine (20 mg, 0.16 mmol) were added, and the resulting solution was stirred for 23 h at room temperature. The reaction was extracted with

ice-cooled 1M HCl, then sat. NaHCO₃. The organic layer was dried over MgSO₄, filtered, and evaporated to yield crude product (241 mg). The crude product was chromatographed on silica gel (30-40% EtOAc/hexanes) to yield the desired product
5 (64 mg, 20%). ¹H NMR (CDCl₃) δ 8.21 (d, 1H, J = 8.1), 7.58 (m, 5H), 7.35 (m, 8H), 7.18 (s, 1H), 4.16 (d, 2H, J = 5.8), 2.59 (s, 3H), 1.33 (s, 9H).

3-(Trifluoromethyl)-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-
10 (N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide trifluoroacetic acid salt: TFA (1 mL) was added to 1-[2-(((t-butoxycarbonyl)amino)methyl)phenyl)-5-(2'-methylsulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-(trifluoromethyl)pyrazole (64 mg, 0.10 mmol) in CH₂Cl₂ (1 mL) and stirred at room
15 temperature for 21 h. The reaction was evaporated and purified by reverse phase prep. HPLC (15-70% MeCN/H₂O/0.5% TFA) to yield the desired product (30 mg, 46%). ¹H NMR (DMSO) d 10.79 (s, 1H), 8.16 (bs, 2H), 8.04 (d, 1H, J = 7.7), 7.77 (s, 1H), 7.71 (td, 1H, J = 5.8), 7.64 (m, 6H), 7.51 (m, 1H),
20 7.45 (d, 1H, J = 7.6), 7.34 (m, 3H), 3.79 (bm, 2H), 2.78 (s, 3H). ¹⁹F NMR (DMSO) d -61.22, -73.97. HRMS calc. C₂₅H₂₂N₄O₃F₃S: 515.1365; found, 515.1359.

Example 32

25 **3-Trifluoromethyl-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxamide•TFA**

1-[2-(((t-Butoxycarbonyl)amino)methyl)phenyl)-5-(2'-(t-butylamino)sulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-(trifluoromethyl)pyrazole: Oxalyl chloride (90 µl, 1.0 mmol) and DMF (2 drops) were added to 1-(2-(((t-butoxycarbonyl)amino)methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl-5-carboxylic acid (Example 31 Part A, 200 mg,
30 0.52 mmol) in CH₂Cl₂ (5 mL) and the resulting solution was stirred for 95 min at room temperature. The solvents were evaporated and the resulting compound was placed briefly under high vacuum before redissolving in CH₂Cl₂ (5 mL).

Triethylamine (150 μ l, 1.1 mmol), 4-amino-2'-(t-butylamino)sulfonyl-[1,1']-biphenyl (190 mg, 0.62 mmol), and 4-dimethylaminopyridine (20 mg, 0.16 mmol) were added, and the resulting solution was stirred for 23 h at room temperature.

5 The reaction was extracted with dilute brine solution, ice-cooled 1M HCl, and sat. NaHCO_3 . The organic layer was dried over MgSO_4 , filtered, and evaporated to yield crude product (371 mg). The crude product was chromatographed on silica gel (30% EtOAc/hexanes) to yield the desired product (74 mg, 21%).

10 ^1H NMR (CDCl_3) δ 8.64 (bs, 1H), 8.15 (dd, 1H, $J = 7.7$, $J' = 1.5$), 7.45 (m, 10H), 7.25 (d, 1H, $J = 6.9$), 7.20 (s, 1H), 5.33 (bs, 1H), 4.15 (d, 2H, $J = 5.8$), 3.49 (bs, 1H), 1.34 (s, 9H), 0.97 (s, 9H).

15 3-Trifluoromethyl-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxyamide trifluoroacetic acid salt: TFA (2 mL) was added to 1-[2-(((t-butoxycarbonyl)amino)methyl)phenyl)-5-(2'-(t-butylamino)sulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-

20 (trifluoromethyl)pyrazole (74 mg, 0.11 mmol) in CH_2Cl_2 (1 mL) and stirred at room temperature for 19 h. Additional TFA (2 mL) was added, and the reaction continued stirring for 3 h. The reaction was evaporated and purified by reverse phase prep. HPLC (15-70% MeCN/ H_2O /0.5% TFA) to yield the desired

25 product (41 mg, 59%). ^1H NMR (DMSO) δ 10.75 (s, 1H), 8.17 (bs, 3H), 7.98 (dd, 1H, $J = 7.3$), 7.76 (s, 1H), 7.57 (m, 7H), 7.44 (d, 1H, $J = 6.7$), 7.32 (d, 2H, $J = 8.8$), 7.25 (m, 3H) 3.79 (bd, 2H, $J = 5.1$). ^{19}F NMR (DMSO) δ -61.22, -73.99. HRMS calc. $\text{C}_{24}\text{H}_{21}\text{N}_5\text{O}_3\text{F}_3\text{S}$: 516.1317; found, 516.1319.

30

Example 33

3-Trifluoromethyl-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxyamide•TFA

35

1-[2-(((t-Butoxycarbonyl)amino)methyl)phenyl)-5-(3-fluoro-2'-(t-butylamino)sulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-(trifluoromethyl)pyrazole: Oxalyl chloride (300 μ l, 3.4 mmol)

and DMF (3 drops) were added to 1-(2-[(t-butoxycarbonyl)amino]methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl-5-carboxylic acid (Example 31 Part A, 888 mg, 2.3 mmol) in CH₂Cl₂ (30 mL) and the resulting solution was stirred
5 for 65 min at room temperature. The solvents were evaporated and the resulting compound was placed briefly under high vacuum before redissolving in CH₂Cl₂ (30 mL). 4-Amino-3-fluoro-2'-(t-butylamino)sulfonyl-[1,1']-biphenyl (890 mg, 2.8 mmol), and 4-dimethylaminopyridine (420 mg, 3.4 mmol) were
10 added, and the resulting solution was stirred for 22 h at room temperature. The reaction was concentrated and chromatographed on silica gel (20-30% EtOAc/hexanes). The fractions containing product were combined and concentrated to half the original volume, then extracted 3x with ice-cooled 1M
15 HCl, 2x with room temperature 1M HCl, sat. NaHCO₃, 2M HCl, and sat. NaHCO₃. The organic layer was dried over Na₂SO₄, filtered, and evaporated to yield the desired product (600 mg, 38%).

20 3-Trifluoromethyl-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxamide trifluoroacetic acid salt: TFA (9 mL) was added to 1-[2-(((t-butoxycarbonyl)amino)methyl)phenyl)-5-(3-fluoro-2'-(t-butylamino)sulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-
25 (trifluoromethyl)pyrazole (600 mg, 0.87 mmol) in CH₂Cl₂ (3 mL) and stirred at room temperature for 18 h. The reaction was evaporated and purified by reverse phase prep. HPLC (10-70% MeCN/H₂O/0.5% TFA) to yield impure product (349 mg). This material was again purified by reverse phase HPLC (5-70%
30 MeCN/H₂O/0.5% TFA) to yield clean product (162 mg, 35%). Any impure fractions containing product were combined and purified by reverse phase HPLC (20-60% MeCN/H₂O/0.5% TFA) to yield additional product (119 mg, 26%) ¹H NMR (DMSO) δ 10.62 (s, 1H), 8.16 (bs, 2H), 7.98 (dd, 1H, J = 7.0, J' = 2.2), 7.79 (s, 1H), 7.54 (m, 7H), 7.39 (s, 2H), 7.28 (m, 2H), 7.15 (d, 1H, J = 8.4), 3.78 (bm, 2H). ¹⁹F NMR (DMSO) δ -61.26, -74.29, -122.79. HRMS calc. C₂₄H₂₀N₅O₃F₄S: 534.1223; found, 534.1216.

Example 34

3-Trifluoromethyl-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide•TFA

- 5 1-[2-(((t-butoxycarbonyl)amino)methyl)phenyl)-5-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-(trifluoromethyl)pyrazole: Oxalyl chloride (320 μ l, 3.7 mmol) and DMF (4 drops) were added to 1-(2-(((t-butoxy
- 10 carbonyl)amino)methyl)phenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl-5-carboxylic acid (Example 31 Part A, 940 mg, 2.4 mmol) in CH_2Cl_2 (35 mL) and the resulting solution was stirred for 55 min at room temperature. The solvents were evaporated and the resulting compound was placed briefly under high vacuum before
- 15 redissolving in CH_2Cl_2 (20 mL). 4-Amino-3-fluoro-2'-methylsulfonyl-[1,1']-biphenyl (750 mg, 2.8 mmol) in CH_2Cl_2 (15 mL), and 4-dimethylaminopyridine (447 mg, 3.7 mmol) were added, and the resulting solution was stirred for 20 h at room temperature. The reaction was concentrated and
- 20 chromatographed on silica gel (30-40% EtOAc/hexanes) to yield impure product (802 mg), which was purified on reverse phase prep. HPLC (10-70% MeCN/ H_2O /0.5% TFA) to yield clean product (645 mg, 42%).
- 25 3-Trifluoromethyl-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide trifluoroacetic acid salt: TFA (2 mL) was added to 1-[2-(((t-butoxycarbonyl)amino)methyl)phenyl)-5-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-
- 30 (trifluoromethyl)pyrazole (132 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) and stirred at room temperature for 5 h. The reaction was evaporated and purified by reverse phase prep. HPLC (10-70% MeCN/ H_2O /0.5% TFA) to yield the desired product (80 mg, 59%). ^1H NMR (DMSO) δ 10.65, (s, 1H), 8.16 (bs, 3H), 8.05 (d, 1H, J =
- 35 6.6), 7.79 (s, 1H), 7.73 (td, 1H, J = 6.2, J' = 1.5), 7.67 (dd, 1H, J = 7.7, J' = 1.5), 7.54 (m, 5H), 7.35 (m, 2H), 7.19 (d, 1H, J = 8.0), 3.78 (bd, 2H, J = 5.5), 2.88 (s, 3H). ^{19}F

NMR (DMSO) δ -61.26, -74.11, -122.19. HRMS calc. C₂₅H₂₁N₄O₃F₄S: 533.1217; found, 533.1258.

Example 35

5 **3-Trifluoromethyl-1-(2-(N-(glycyl)aminomethyl)phenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide•TFA**

The title compound was prepared from 1-[2-
10 ((aminomethyl)phenyl)-5-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-(trifluoromethyl)pyrazole trifluoroacetic acid salt (prepared in Example 34) and N-Boc glycine according to the procedure in Example 29; HRMS (M+H)⁺: 590.1495 m/z.

15

Example 36

3-Trifluoromethyl-1-(2-((N-(N-
methylglycyl)aminomethyl)phenyl)-1H-pyrazole-5-(N-(3-
fluoro-2'-methylsulfonyl-[1,1']-biphen-4-
20 yl))carboxamide•TFA

The title compound was prepared from 1-[2-
((aminomethyl)phenyl)-5-(3-fluoro-2'-methylsulfonyl-[1,1']-
biphen-4-yl))aminocarbonyl]-3-(trifluoromethyl)pyrazole
25 trifluoroacetic acid salt (prepared in Example 34) and N-Boc-N-methyl glycine according to the procedure in Example 29; HRMS (M+H)⁺: 604.1655 m/z.

Example 37

30 **3-Trifluoromethyl-1-(2-carboxamidophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide**

Methyl 2-[5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-
35 yl]benzoate: 2-[5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzoic acid (Example 31 Part A, 26.5 g, 82 mmol) was dissolved in SOCl₂ (130 mL) and heated at reflux for 2.5 h. Excess SOCl₂ was evaporated, and the residual acid chloride was

placed under high vacuum. The acid chloride was cooled to 0°C, and dry MeOH (130 mL) was added. The resulting solution was allowed to warm slowly to room temperature, then stirred at room temperature for 22 h. The solvent was evaporated, and the crude product was chromatographed on silica gel (0-30% EtOAc/hexanes) to yield the desired product (22.6 g, 82%). ¹H NMR (CDCl₃) δ 8.10 (dd, 1H, J = 7.3, J' = 1.9), 7.67 (m, 2H), 7.50 (dd, 1H, J = 7.7, J' = 1.4), 7.37 (s, 1H), 6.92 (s, 1H), 6.29 (m, 1H), 5.77 (d, 1H, J = 3.3), 3.62 (s, 3H).

10

1-(2-Carbomethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-5-carboxylic acid: A 5% aq. solution of NaH₂PO₄ (320 mL) and water (200 mL) were added to methyl 2-[5-(2-furyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzoate (23.7 g, 71 mmol) in t-BuOH (470 mL). The reaction was immersed in a room temperature water bath, and solid KMnO₄ (55.8 g, 353 mmol) was added portionwise over 1 h. The reaction was heated at 70°C for 90 min, cooled, and filtered through celite. The celite was rinsed with acetone and EtOAc. The filtrate was concentrated to remove most of the organics, then extracted with EtOAc. The organic layer was extracted with sat. Na₂SO₃, dried over Na₂SO₄, filtered, evaporated, and set aside. The aqueous layers were combined and neutralized to pH 6.5 with 2M HCl (100 mL), and then extracted with EtOAc (3x). The organic layers were combined, dried over Na₂SO₄, filtered, and evaporated to yield clean product (14.8 g, 67%). ¹H NMR (CDCl₃) δ 8.10 (dd, 1H, J = 7.3, J' = 1.5), 7.64 (m, 2H), 7.42 (dd, 1H, J = 7.3, J' = 1.1), 7.31 (s, 1H), 3.69 (s, 3H).

1-[2-Carbomethoxyphenyl-5-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl)]aminocarbonyl]-3-(trifluoromethyl)pyrazole: Oxalyl chloride (2.9 mL, 33 mmol) and DMF (10 drops) were added to 1-(2-carbomethoxyphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-5-carboxylic acid (7.0 g, 22 mmol) in dry CH₂Cl₂ (240 mL), and the resulting solution was stirred at room temperature for 80 min. The solvents were evaporated, and the resulting compound was placed briefly under high vacuum before redissolving in CH₂Cl₂ (240 mL). 4-Amino-3-fluoro-2'-

methylsulfonyl-[1,1']-biphenyl hydrochloride (7.4 g, 25 mmol) and 4-dimethylaminopyridine (7.1 g, 58 mmol) were added, and the resulting solution was stirred at room temperature for 67 h. The reaction was extracted with 1M HCl (2x), then sat.

5 NaHCO₃. The organic layer was dried over MgSO₄, filtered, and evaporated to yield crude product. The crude product was chromatographed on silica gel (30-50% EtOAc/hexanes) to yield the desired product (12.4 g, 99%). ¹H NMR (CDCl₃) δ 8.29 (t, 1H, J = 8.1), 8.21 (m, 2H), 8.11 (dd, 1H, J = 7.7, J' = 1.5),
10 7.62 (m, 5H), 7.30 (m, 2H), 7.14 (m, 2H), 3.77 (s, 3H), 2.69 (s, 3H).

1-[2-Carboxyphenyl-5-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-(trifluoromethyl)pyrazole: 1M
15 LiOH (34 mL) was added to 1-[2-carbomethoxyphenyl-5-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-(trifluoromethyl)pyrazole (12.0 g, 21 mmol) in THF (285 mL) and stirred at room temperature for 26 h. Additional 1M LiOH (15 mL) was added, and the reaction continued stirring for 18
20 h. The resulting solution was heated at 35°C for 2.5 h, then at 50°C for 18 h. The reaction was cooled, concentrated, and partitioned between Et₂O and water. The organic layer was extracted again with water (2x). A small amount of white solid was assumed to be product, and was added to the aqueous
25 layer. The aqueous layers were combined, neutralized to pH 7 with 2M HCl (23 mL), and extracted with EtOAc. Additional 2M HCl (2 mL) was added to the aqueous, which was extracted twice with EtOAc. The EtOAc layers were combined, dried over Na₂SO₄, filtered, and evaporated to yield the desired product (10.3 g,
30 88%). ¹H NMR (CDCl₃) δ 8.21 (m, 4H), 7.75 (m, 1H), 7.60 (m, 4H), 7.29 (m, 3H), 7.13 (m, 2H), 2.70 (s, 3H).

3-Trifluoromethyl-1-(2-carboxamidophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide: 1-
35 [2-Carboxyphenyl-5-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-(trifluoromethyl)pyrazole (3.0 g, 5.5 mmol) was dissolved in SOCl₂ (10 mL) and heated at reflux for 2 h. Excess SOCl₂ was evaporated, and the residual acid chloride

was placed under high vacuum. The acid chloride was dissolved in dry CH_2Cl_2 and cooled to 0°C , and conc. aq. NH_3 (2.0 mL) was added over 20 min. The resulting mixture was stirred at room temperature for 18 h. The reaction was diluted with CH_2Cl_2 and extracted with water. The aqueous layer was extracted with CHCl_3 , $\text{MeOH}/\text{CH}_2\text{Cl}_2$, and CH_2Cl_2 . All of the organics were combined and extracted with sat. NaHCO_3 (2x), 1M HCl , and sat. NaCl . The organic layer was dried over MgSO_4 , filtered, evaporated, and chromatographed on silica gel (30-75% $\text{EtOAc}/\text{hexanes}$) to yield the desired product (794 mg, 27%). ^1H NMR (CDCl_3 , 400 MHz) δ 9.53 (bs, 1H), 8.25 (t, 1H, $J = 8.3$), 8.20 (dd, 1H, $J = 7.8$, $J' = 1.2$), 7.75 (m, 1H), 7.60 (m, 4H), 7.45 (m, 1H), 7.29 (dd, 1H, $J = 7.6$, $J' = 1.2$), 7.20 (dd, 1H, $J = 11.2$, $J' = 1.9$), 7.12 (m, 2H), 6.13 (bs, 1H), 5.68 (bs, 1H), 2.67 (s, 3H).

Example 38

3-Trifluoromethyl-1-(2-cyanophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide

1-[2-Cyanophenyl-5-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-(trifluoromethyl)pyrazole: 1-[2-Carboxamidophenyl-5-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))aminocarbonyl]-3-(trifluoromethyl)pyrazole (Example 36, 715 mg, 1.3 mmol) and triethylamine (360 μL , 2.6 mmol) were combined in dry CH_2Cl_2 (10 mL) and cooled to 0°C . Trichloroacetyl chloride (160 μL , 1.4 mmol) was added over 5 min.. The resulting solution was stirred at 0°C for 30 min, then at room temperature for 2 h. Additional triethylamine (200 μL , 1.4 mmol) was added, and the reaction continued stirring at room temperature for 68 h. Additional trichloroacetyl chloride (20 μL , 0.2 mmol) was added. After stirring 2 h, the reaction was quenched with water. The organic layer was removed and extracted with 1M HCl and sat. NaHCO_3 . A small amount of sat. NaCl was added to break up the emulsion. The organic layer was dried over Na_2SO_4 , filtered, evaporated, and chromatographed on silica gel (20-75%

EtOAc/hexanes) to yield the desired product (114 mg, 17%). ¹H NMR (CDCl₃) δ 8.25 (m, 2H), 8.09 (bs, 1H), 7.82 (m, 2H), 7.65 (m, 4H), 7.35 (m, 2H), 7.20 (m, 2H), 2.72 (s, 3H).

5

Example 39

1-(2'-Aminomethylphenyl)-5-[[(2'-methylsulfonyl)-3-fluoro-[1,1']-biphen-4-yl]aminocarbonyl]-tetrazole TFA salt

10 Ethyl 1-(2-cyanophenyl)-5-tetrazole carboxylate: To a solution of anthranilonitrile (10.00 g) and Et₃N (13.21 mL) in CH₂Cl₂ (250 mL) was added ethyloxalyl chloride (9.92 mL) in a dropwise fashion over 30 minutes. The reaction was stirred at RT under N₂ for 3 h. The reaction mixture was filtered. The
15 filtrate was washed with water (2 x 150 mL) and brine (1 x 150 mL), filtered through phase separatory paper and evaporated. The residue was dissolved in 60 mL of CH₂Cl₂ and 300 mL of hexane was added. The solution was allowed to stand at RT for the weekend. The precipitate was filtered, rinsed with
20 hexane, and dried under vacuum to give 17.74 g of 1-(2-cyanophenyl)-oxoacetic acid ethyl ester.

A solution of triphenylphosphine (16.83 g) in CCl₄ (100 mL) was stirred at 0° C for 30 minutes. 1-(2-Cyanophenyl)-
25 oxoacetic acid ethyl ester (7.00 g) in CCl₄ (100 mL) was added and the reaction was stirred at reflux under N₂ for 16 h. The reaction was cooled to RT and the precipitate filtered off. The filtrate was evaporated and dissolved in CH₃CN (300 mL). Sodium azide (2.29 g) was added and the reaction stirred at RT
30 under N₂ for 16 h. The solvent was evaporated and the residue taken up in EtOAc (100 mL). The organic solution was washed with water (2 x 100 mL) and brine (1 x 100 mL), dried over MgSO₄, and evaporated. The crude material was purified by silica gel chromatography eluting with CH₂Cl₂ to give 3.80 g
35 of the title compound; LRMS (ES⁺) M⁺: 244 m/z

1-(2'-Aminomethylphenyl)-5-[[(2'-methylsulfonyl)-3-fluoro-[1,1']-biphen-4-yl]aminocarbonyl]-tetrazole: To a solution of

[(2'-methylaminosulfonyl)-3-fluoro-[1,1']-biphen-4-yl]amine (0.32 g) in anhydrous CH₂Cl₂ (10 mL) was added trimethylaluminum (2.12 mL, 2M in heptane). The reaction was stirred at RT under N₂ for 30 minutes. A solution of ethyl 1-(2-cyanophenyl)-5-tetrazole carboxylate (0.28 g) in anhydrous CH₂Cl₂ (10 mL) was added and the reaction was stirred at RT under N₂ for 64 h. The reaction was quenched with 5 drops of 1N HCl and diluted with CH₂Cl₂ (30 mL). The organic solution was washed with water (2 x 25 mL) and brine (1 x 25 mL), filtered through phase separatory paper, and evaporated. The crude material was purified by silica gel chromatography eluting with 10% EtOH/CH₂Cl₂ to give 0.35 g of 1-(2'-cyanophenyl)-5-[[[(2'-methylsulfonyl)-3-fluoro-[1,1']-biphen-4-yl]aminocarbonyl]-tetrazole; LMRS (ES⁻) M⁻: 461 m/z.

Cobalt chloride (0.098 g) was added to 1-(2'-cyanophenyl)-5-[[[(2'-methylsulfonyl)-3-fluoro-[1,1']-biphen-4-yl]aminocarbonyl]-tetrazole (0.35 g) and sodium borohydride (0.072 g) in DMF (5 mL). The reaction was stirred at room temperature for 16 h. The resulting mixture was stirred at room temperature for 16 h. 6M HCl (5 mL) was added over 5 min. The quenched reaction was stirred at room temperature for 3.5 h, diluted with EtOAc and water. The resulting emulsion was filtered through celite, and the organic layer was washed with 1N HCl, dried over Na₂SO₄, filtered, and evaporated to yield crude product (100 mg). The aqueous layers were combined and neutralized (pH 7) with saturate NaHCO₃, extracted with EtOAc. The organic layers were combined, dried over Na₂SO₄, filtered, and evaporated to yield a second batch of crude product. The two batches of crude product were combined and purified by reverse phase HPLC (10-90% MeCN/H₂O/0.5% TFA) to yield 102 mg of the title compound as its TFA salt. LMRS (ES⁺) M⁺: 467 m/z.

35

Example 40

1-(2'-Aminomethylphenyl)-5-[(2'-aminosulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]-tetrazole•TFA

The title compound was prepared in an analogous fashion as its TFA salt. LRMS (ES⁺) M⁺: 468 m/z.

Example 41

- 5 1-[2-(Aminomethyl)phenyl]-3-thiomethoxy-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole•TFA

Methyl 3-(thiomethoxy)pyrazole-5-carboxylate: A mixture of
10 methyl 4,4-bis(thiomethoxy)-2-oxo-3-butenate (9.9 g, 48 mmol) and hydrazine monohydrate (2.6 mL, 53 mmol) in 200 mL of glacial acetic acid was stirred at 100 °C for 18 h. The reaction was cooled and concentrated. The residue was taken up in ethyl acetate, washed with sat'd aq NaHCO₃ and brine,
15 dried (MgSO₄) and concentrated. The solid residue was recrystallized from hexanes/ethyl acetate to afford 6.0 g (73%) of the title compound. ¹H NMR (CDCl₃) δ 11.0 (broad s, 1H), 6.74 (s, 1H), 3.88 (s, 3H), 2.48 (s, 3H).

20 Methyl 1-[2-formylphenyl]-3-(thiomethoxy)pyrazole-5-carboxylate: To a solution of methyl 3-(thiomethoxy)pyrazole-5-carboxylate (0.87 g, 5.05 mmol) in 20 mL of 1,4-dioxane was added 2-formylphenyl boronic acid (1.13 g, 7.58 mmol), pyridine (0.82 mL, 10.1 mmol), crushed 4 Å molecular sieves
25 and cupric acetate (1.38 g, 7.58 mmol). The flask was equipped with a drying tube and the mixture was allowed to stir at ambient temperature under an air atmosphere for 18 h. The mixture was filtered through a pad of Celite and concentrated. The residue was purified by flash
30 chromatography to afford 0.22 g (16%) of the title compound. ¹H NMR (CDCl₃) δ 9.66 (s, 1H), 8.02 (dd, 1H), 7.69 (td, 1H), 7.63 (t, 1H), 7.42 (d, 1H), 6.96 (s, 1H), 3.75 (s, 3H), 2.55 (s, 3H).

35 1-[(2-(Hydroxymethyl)phenyl)-3-thiomethoxy-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole: To a solution of methyl 1-[2-formylphenyl]-3-(thiomethoxy)pyrazole-5-carboxylate (0.48 g, 1.74 mmol) in 15

mL of methanol at 0°C was added sodium borohydride (33 mg, 0.87 mmol). The cooling bath was removed and the reaction was stirred for 10 min and then quenched by dilution with water. The reaction mixture was extracted with ethyl acetate and the organics were washed with brine, dried (MgSO₄) and concentrated to afford 0.41 g (85%) of about a 2:1 mixture of a hydroxy ester and a seven-membered ring lactone. This mixture was used without purification. To a solution of (2-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl)amine hydrochloride (0.89 g, 2.94 mmol) in methylene chloride was added trimethylaluminum (2.95 mL of a 2.0 M solution in hexanes, 5.89 mmol) dropwise. This solution was stirred until gas evolution ceased (15-20 min) and then there was added the hydroxy ester/lactone mixture from above (0.41 g, 1.47 mmol) in methylene chloride. The resulting solution was allowed to stir at reflux for 4 h and then it was cooled and quenched by dropwise addition of sat'd aq ammonium chloride. The mixture was diluted with ethyl acetate, the layers were separated, the organic layer was washed with water and brine, dried (MgSO₄) and concentrated. The solid residue was purified by flash chromatography (elution with 1:1 hexanes/ethyl acetate) to afford 0.68 g (91%) of the title compound. LRMS (ES⁺): 534.1 (M+Na)⁺.

1-[(2-(Bromomethyl)phenyl)-3-thiomethoxy-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole: To a solution of 1-[(2-(hydroxymethyl)phenyl)-3-thiomethoxy-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole (0.68 g, 1.3 mmol) in 20 mL of methylene chloride was added carbon tetrabromide (1.06 g, 3.2 mmol) and triphenylphosphine (0.84 g, 3.2 mmol). The resulting solution was stirred at ambient temperature for 4 h. The reaction was diluted with ethyl acetate, washed with water and brine, dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (elution with 3:1 hexanes/ethyl acetate) to afford 0.60 g (81%) of the title compound.

1-[(2-(Azidomethyl)phenyl)-3-thiomethoxy-5-[(2-fluoro)-(2'-methysulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole: To a solution of 1-[(2-(bromomethyl)phenyl)-3-thiomethoxy-5-[(2-fluoro)-(2'-methysulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole (0.42 g, 0.73 mmol) in 5 mL of N,N-dimethylformamide was added sodium azide (0.38 g, 5.85 mmol). This mixture was stirred at ambient temperature for 1 h and then was diluted with ethyl acetate. The organics were washed with water and brine, dried (MgSO₄) and concentrated to afford 0.38 g (97%) of the title compound which was used directly without purification. LRMS (ES⁺): 559.1 (M+Na)⁺.

1-[2-(Aminomethyl)phenyl]-3-thiomethoxy-5-[(2-fluoro)-(2'-methysulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole, trifluoroacetic acid salt: To a solution of 1-[(2-(azidomethyl)phenyl)-3-thiomethoxy-5-[(2-fluoro)-(2'-methysulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole (0.38 g, 0.71 mmol) in 10 mL of methanol was added tin (II) chloride (0.80 g, 4.24 mmol). The reaction mixture was stirred at reflux for 1 h and then was cooled to room temperature and diluted with ethyl acetate. The organics were washed with 5% aq sodium hydroxide and brine, dried (MgSO₄) and concentrated. The residue was purified by preparative HPLC (C18 reverse phase column, elution with a H₂O/CH₃CN gradient with 0.5% TFA) and lyophilized to afford 230 mg (52%) of the title compound as a white powder. LRMS (ES⁺): 511.1 (M+H)⁺.

Example 42

1-[2-(aminomethyl)phenyl]-3-methysulfonyl-5-[(2-fluoro)-(2'-methysulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole•TFA

1-[(2-(Bromomethyl)phenyl)-3-methysulfonyl-5-[(2-fluoro)-(2'-methysulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole: To a solution of 1-[(2-(bromomethyl)phenyl)-3-thiomethoxy-5-[(2-fluoro)-(2'-methysulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole (85 mg, 0.15 mmol) in 10 mL of methylene chloride was added *m*-chloroperoxybenzoic acid (130

mg of 57-86% pure material, ~0.5 mmol). The resulting solution was stirred at ambient temperature for 3 h. The reaction was diluted with ethyl acetate, washed with sat'd aq NaHCO₃ and brine, dried (MgSO₄) and concentrated to afford 80
5 mg (88%) of the title compound which was sufficiently pure to be used without purification.

1-[(2-(Azidomethyl)phenyl)-3-methylsulfonyl-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole: To
10 a solution of 1-[(2-(bromomethyl)phenyl)-3-methylsulfonyl-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole (55 mg, 0.09 mmol) in 1 mL of dimethylsulfoxide was added sodium azide (30 mg, 0.45 mmol). This mixture was stirred at ambient temperature for 1 h and
15 then was diluted with ethyl acetate. The organics were washed with water and brine, dried (MgSO₄) and concentrated to afford 50 mg (97%) of the title compound which was used directly without purification. LRMS (ES⁺): 591.1 (M+Na)⁺.

20 1-[2-(Aminomethyl)phenyl]-3-methylsulfonyl-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole, trifluoroacetic acid salt: To a solution of 1-[(2-(azidomethyl)phenyl)-3-methylsulfonyl-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole (90
25 mg, 0.16 mmol) in 4 mL of methanol was added tin (II) chloride (0.30 g, 1.6 mmol). The reaction mixture was stirred at reflux for 1 h and then was cooled to room temperature and diluted with ethyl acetate. The organics were washed with 5% aq sodium hydroxide and brine, dried (MgSO₄) and concentrated.
30 The residue was purified by preparative HPLC (C18 reverse phase column, elution with a H₂O/CH₃CN gradient with 0.5% TFA) and lyophilized to afford 18 mg (17%) of the title compound as a white powder. LRMS (ES⁺): 543.2 (M+H)⁺.

35

Example 43

1-[2-(aminomethyl)phenyl]-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]triazole•TFA

2-Azidobenzyl alcohol: To a solution of 2-aminobenzyl alcohol (12.0 g, 97.4 mmol) in 50 mL of trifluoroacetic acid at 0°C was added sodium nitrite (7.39 g, 107.2 mmol). This solution was stirred for 45 min and then there was added sodium azide (6.33 g, 97.4 mmol) dropwise as a solution in water. The resulting mixture was stirred at 0°C for 45 min and then was carefully quenched by slow addition of potassium carbonate. The reaction mixture was diluted with ethyl acetate, washed with brine, dried (MgSO₄), filtered through a pad of silica gel and concentrated to afford 10.5 g (72%) of the title compound which was used without further purification. ¹H NMR (CDCl₃) δ 7.33 (m, 2H), 7.14 (m, 2H), 4.59 (s, 2H), 2.69 (broad s, 1H).

(2-Azidophenyl)methyl propiolate: To a solution of 2-azidobenzyl alcohol (15.66 g, 105.1 mmol) in 200 mL of methylene chloride was added propiolic acid (7.1 mL, 115.6 mmol), dicyclohexylcarbodiimide (20.0 g, 110.3 mmol) and 4-dimethylaminopyridine (1.93 g, 15.8 mmol). The resulting mixture was allowed to stir at ambient temperature for 18h. The mixture was filtered, concentrated and the residue was purified by flash chromatography (elution with 1:1 hexanes/ethyl acetate) to afford 10.7 g (51%) of the title compound. ¹H NMR (CDCl₃) δ 7.40 (m, 2H), 7.17 (m, 2H), 5.20 (s, 2H), 2.92 (s, 1H).

Triazololactone: A solution of (2-azidophenyl)methyl propiolate (10.7 g, 53.2 mmol) in 100 mL of toluene was stirred at 100°C for 18 h. The reaction was cooled and concentrated and the residue was purified by flash chromatography (elution with 1:1 hexanes/ethyl acetate) to afford 1.4 g (13%) of the title compound. ¹H NMR (CDCl₃) δ 8.38 (s, 1H), 8.04 (d, 1H), 7.63 (m, 1H), 7.54 (m, 2H), 5.16 (s, 2H).

1-[(2-(Hydroxymethyl)phenyl)-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]triazole: To a solution of (2-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl)amine

hydrochloride (2.10 g, 6.96 mmol) in methylene chloride was added trimethylaluminum (20.8 mL of a 2.0 M solution in hexanes, 41.8 mmol) dropwise. This solution was stirred until gas evolution ceased (about 30 min) and then there was added
5 the triazololactone from above (1.40 g, 6.96 mmol) as a solution in methylene chloride. The resulting solution was allowed to stir at reflux for 18 h and then it was cooled and quenched by dropwise addition of sat'd aq ammonium chloride. The mixture was diluted with ethyl acetate, the layers were
10 separated, the organic layer was washed with water and brine, dried (MgSO₄) and concentrated. The solid residue was purified by flash chromatography (elution with 3:1 ethyl acetate/hexanes) to afford 1.0 g (31%) of the title compound. LRMS (ES⁺): 467.2 (M+H)⁺.

15
1-[(2-(Bromomethyl)phenyl)-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]triazole: To a solution of 1-[(2-(hydroxymethyl)phenyl)-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]triazole (0.80 g, 1.71 mmol)
20 in 20 mL of methylene chloride was added carbon tetrabromide (2.83 g, 8.55 mmol) and triphenylphosphine (2.24 g, 8.55 mmol). The resulting solution was stirred at ambient temperature for 18 h. The reaction was diluted with ethyl acetate, washed with water and brine, dried (MgSO₄) and
25 concentrated. The residue was purified by flash chromatography (elution with 1:1 hexanes/ethyl acetate) to afford 0.80 g (89%) of the title compound. LRMS (ES⁺): 529.1/531.1 (M+H)⁺.

30 1-[(2-(Azidomethyl)phenyl)-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]triazole: To a solution of 1-[(2-(bromomethyl)phenyl)-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]triazole (0.25 g, 0.47 mmol)
35 in 10 mL of N,N-dimethylformamide was added sodium azide (0.37 g, 5.6 mmol). This mixture was stirred at 65°C for 18 h and then was cooled and diluted with ethyl acetate. The organics were washed with water and brine, dried (MgSO₄) and concentrated to afford 0.22 g (96%) of the title compound

which was used directly without purification. LRMS (ES+):
514.2 (M+Na)⁺.

1-[2-(Aminomethyl)phenyl]-5-[(2-fluoro)-(2'-methylsulfonyl-
5 [1,1']-biphen-4-yl)aminocarbonyl]triazole, trifluoroacetic
acid salt: To a solution of 1-[(2-(azidomethyl)phenyl)-5-[(2-
fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-
yl)aminocarbonyl]triazole (0.22 g, 0.45 mmol) in 10 mL of
absolute ethanol was added 10% palladium on carbon catalyst
10 (25 mg) and concentrated HCl (0.04 mL, 0.45 mmol). The
reaction mixture was stirred at ambient temperature under 1
atm of hydrogen for 2 h and then was filtered through a pad of
Celite and concentrated. The residue was purified by
preparative HPLC (C18 reverse phase column, elution with a
15 H₂O/CH₃CN gradient with 0.5% TFA) and lyophilized to afford 26
mg (10%) of the title compound as a white powder. LRMS (ES+):
466.2 (M+H)⁺.

Example 44

20 1-[2-(Aminomethyl)phenyl]-5-[(2-fluoro)-(2'-
methylsulfonyl)-[1,1']-biphen-4-
yl)aminocarbonyl]pyrazole•TFA

Methyl 1-[2-methylphenyl]pyrazole-5-carboxylate: A neat
25 mixture of methyl pyruvate (11.37 mL, 125.9 mmol) and
dimethylformamide dimethylacetal (16.72 mL, 125.9 mmol) was
stirred at 80°C for 24 h. The mixture was cooled and
concentrated. A portion of the residue (4.00 g, 25.45 mmol)
was dissolved in 50 mL of glacial acetic acid and then there
30 was added o-tolylhydrazine hydrochloride (4.44 g, 27.99 mmol).
This mixture was stirred at 100°C for 18 h and then was cooled
and concentrated. The residue was dissolved in ethyl acetate,
washed with sat'd aq sodium carbonate and brine, dried (MgSO₄)
and concentrated. The residue was purified by flash
35 chromatography (elution with 2:1 hexanes/ethyl acetate) to
afford 3.0 g (55%) of the title compound. ¹H NMR (CDCl₃) δ
7.70 (d, 1H), 7.4-7.2 (m, 4H), 7.00 (d, 1H), 3.71 (s, 3H),
2.00 (s, 3H).

Methyl 1-[2-(bromomethyl)phenyl]pyrazole-5-carboxylate: To a solution of methyl 1-[2-methylphenyl]pyrazole-5-carboxylate (1.00 g, 4.62 mmol) in 20 mL of carbon tetrachloride was added
5 N-bromosuccinimide (0.823 g, 4.62 mmol) and AIBN (76 mg, 0.46 mmol). This mixture was stirred at 80°C for 18 h. The volatiles were removed and the residue was taken up in ether, filtered through a pad of silica gel and concentrated to afford 1.3 g (95%) of the title compound which was used
10 without further purification. LRMS (ES+): 295.0/297.0 (M+H)⁺.

Methyl 1-[2-(azidomethyl)phenyl]pyrazole-5-carboxylate: To a solution of methyl 1-[2-(bromomethyl)phenyl]pyrazole-5-carboxylate (1.30 g, 4.40 mmol) in 10 mL of N,N-
15 dimethylformamide was added sodium azide (2.86 g, 44.0 mmol). This mixture was stirred at ambient temperature for 48 h and then was diluted with ethyl acetate. The organics were washed with water and brine, dried (MgSO₄) and concentrated to afford 0.80 g (71%) of the title compound which was used directly
20 without purification. LRMS (ES+): 280.1 (M+Na)⁺.

1-[(2-(Azidomethyl)phenyl)-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole: To a solution of (2-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl)amine
25 hydrochloride (0.94 g, 3.11 mmol) in 20 mL of methylene chloride was added trimethylaluminum (4.67 mL of a 2.0 M solution in hexanes, 9.33 mmol) dropwise. This solution was stirred until gas evolution ceased (about 30 min) and then there was methyl 1-[2-(azidomethyl)phenyl]pyrazole-5-
30 carboxylate (0.80 g, 3.11 mmol) as a solution in methylene chloride. The resulting solution was allowed to stir at reflux for 18 h and then it was cooled and quenched by dropwise addition of sat'd aq ammonium chloride. The mixture was diluted with ethyl acetate, the layers were separated, the
35 organic layer was washed with water and brine, dried (MgSO₄), filtered through a pad of silica gel and concentrated to afford 1.0 g (67%) of the title compound. LRMS (ES+): 513.0 (M+Na)⁺.

1-[2-(Aminomethyl)phenyl]-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole, trifluoroacetic acid salt: To a solution of 1-[(2-(azidomethyl)phenyl)-5-[(2-fluoro)-(2'-methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole (0.50 g, 1.0 mmol) in 20 mL of absolute ethanol was added 10% palladium on carbon catalyst (50 mg) and concentrated HCl (0.085 mL, 1.0 mmol). The reaction mixture was stirred at ambient temperature under 1 atm of hydrogen for 2 h and then was filtered through a pad of Celite and concentrated. The residue was purified by preparative HPLC (C18 reverse phase column, elution with a H₂O/CH₃CN gradient with 0.5% TFA) and lyophilized to afford 60 mg (10%) of the title compound as a white powder. LRMS (ES⁺): 465.2 (M+H)⁺.

Example 45

1-[2-(Aminomethyl)phenyl]-3-trifluoromethyl-5-[(2-fluoro)-(2'-pyrrolidinomethyl)-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole•TFA

Part A: 2-Fluoro-4-((2'-tert-butylldimethylsilyloxymethyl)phenyl)aniline: A solution of 2-formylphenylboronic acid (5 g, 33.3 mmol) and 4-bromo-2-fluoroaniline (4.2 g, 22.2 mmol) in THF (80 mL) and aqueous Na₂CO₃ solution (2M, 80 mL) was bubbled with nitrogen for 10 minutes. After Pd(PPh₃)₄ (1.54 g, 1.33 mmol) was added, the resulting mixture was refluxed under nitrogen for 4 hours. The THF layer was separated and filtered through a pad of silica gel. The silica gel was washed with THF. To the combined filtrates containing 2-fluoro-4-(2'-formylphenyl)aniline (65 mL) was portion by portion added NaBH₄ (2.2 g, 29.1 mmol). The resulting mixture was stirred at room temperature for 1 hour, quenched with 1N HCl (10 mL), and washed with 1N HCl (100 mL x 3). The combined HCl layers were neutralized with 50% NaOH to pH 12 and extracted with EtOAc (100 mL x 3). The EtOAc layers were dried over Na₂SO₄, concentrated, and purified by column chromatography with a

graduate solvent (hexane to EtOAc) to give 2-fluoro-4-(2'-hydroxymethylphenyl)aniline (3.83 g, 97.6%). ^1H NMR (CDCl_3) δ 7.53 (dd, $J = 6.6$ Hz, $J = 2.2$ Hz, 1H), 7.36-7.33 (m, 2H), 7.25 (dd, $J = 6.6$ Hz, $J = 2.2$ Hz, 1H), 7.06 (dd, $J = 12.1$ Hz, $J = 1.8$ Hz, 1H), 6.97 (dd, $J = 8.0$ Hz, $J = 1.8$ Hz, 1H), 6.82 (t, $J = 8.8$ Hz, 1H), 4.63 (s, 2H), 3.79 (bs, 2H); ^{19}F NMR (CDCl_3): δ -135.66 (dd, $J = 12.21$ Hz, $J = 9.2$ Hz); CIMS(CI) m/z 218 (M+H, 100%).

To a solution of 2-fluoro-4-(2'-hydroxymethylphenyl)aniline (5 g, 23 mmol) in THF (150 mL) was added imidazole (2.35 g, 34.5 mmol) and 2'-tert-butylldimethylsilylchloride (5.18 g, 34.5 mmol), and the resulting mixture was stirred at room temperature for 24 hours. The mixture was diluted with hexane (150 mL) and washed with water (150 mL). The organic layer was washed with brine, dried over MgSO_4 , purified by column chromatography with hexane and methylenechloride (1 to 1) to give 2-fluoro-4-((2'-tert-butylldimethylsilyloxymethyl)phenyl)aniline (7.1 g, 92.8%) as a colorless oil. ^1H NMR (CDCl_3) δ 7.55 (dd, $J = 7.7$ Hz, $J = 1.1$ Hz, 1H), 7.35 (dd, $J = 7.4$ Hz, $J = 1.9$ Hz, 1H), 7.30 (dd, $J = 9.1$ Hz, $J = 1.4$ Hz, 1H), 7.20 (dd, $J = 7.3$ Hz, $J = 1.5$ Hz, 1H), 7.05 (dd, $J = 12.1$ Hz, $J = 1.8$ Hz, 1H), 6.93 (dd, $J = 8.0$ Hz, $J = 1.4$ Hz, 1H), 6.80 (dd, $J = 9.1$ Hz, $J = 8.0$ Hz, 1H), 4.60 (s, 2H), 3.77 (bs, 2H), 0.91 (s, 9H), 0.04 (s, 6H); ^{19}F NMR (CDCl_3): δ -136.04; CIMS: 332 (M+H, 100).

Part B: 1-(2-cyanophenyl)-5-furyl-3-trifluoromethylpyrazole:
To a solution of 4,4,4-trifluoro-1-(2-furyl)-1,3-butanedione (2.06 g, 10 mmol) in ethanol (mL) was added hydrazine monohydrate (0.46 g, 10 mmol). The resulting mixture was refluxed for 16 hours and dried under vacuum to give 5-furyl-3-trifluoromethyl-3-hydroxypyrazoline in almost quantitative yield. ^1H NMR (CDCl_3) δ 7.48 (d, $J = 1.9$ Hz, 1H), 6.63 (d, $J = 3.7$ Hz, 1H), 6.47 (dd, $J = 3.7$ Hz, $J = 1.9$ Hz, 1H), 6.16 (s, 1H), 3.48 (d, $J = 17.9$ Hz, 1H), 3.18 (d, $J = 17.9$ Hz, 1H); ^{19}F NMR (CDCl_3): δ -81.47; ESMS(+): 221 (M+H, 100).

To a solution of 2-fluorobenzonitrile (0.605 g, 5 mmol) and 5-furyl-3-trifluoromethyl-3-hydroxypyrazoline (1.1 g, 5

mmol) in DMF (10 mL) was added Cs₂CO₃ (1.63 g, 5 mmol), and the resulting mixture was stirred at 110 °C for 16 hours. The mixture was diluted with EtOAc, washed with brine (x 5), dried over MgSO₄, and purified by column chromatography with a
5 gradient solvent (hexane to ethyl acetate) to give 1-(2-cyanophenyl)-5-furyl-3-trifluoromethylpyrazole and 1-(2-cyanophenyl)-3-furyl-5-trifluoromethylpyrazole (1.27 g, 83.8 %) in a ratio of 95 to 5. ¹H NMR (CDCl₃) δ 7.82 (dd, J = 7.7 Hz, J = 1.5 Hz, 1H), 7.77 (dd, J = 7.7 Hz, J = 1.5 Hz, 1H),
10 7.66 (td, J = 7.7 Hz, J = 1.1 Hz, 1H), 7.61 (d, J = 7.7 Hz, 1H), 7.39 (d, J = 1.4 Hz, 1H), 6.96 (s, 1H), 6.37 (dd, J = 3.3 Hz, J = 1.4 Hz, 1H), 6.04 (d, J = 3.3 Hz, 1H); ¹⁹F NMR (CDCl₃): δ - 62.98; ESMS(+): 304 (M+H, 100).

15 Part C: 1-(2-(N-Boc-aminomethyl)phenyl)-3-trifluoromethylpyrazol-5-yl-carboxylic acid: To a solution of 1-(2-cyanophenyl)-5-furyl-3-trifluoromethylpyrazole (1.5 g, 4.67 mmol) in DMF (20 mL) was portion by portion added NaBH₄ (0.71 g, 18.7 mmol) and then CoCl₂ (0.61 g, 4.67 mmol) at 0 °C.
20 After the resulting mixture was stirred at room temperature for 18 hours, a black suspension was cooled to 0 °C and carefully acidified with 6N HCl (20 mL). The resulting mixture was stirred at room temperature for 3 hours, and neutralized with 1N NaOH to pH 14. The mixture was diluted
25 with EtOAc (100 mL), and filtered through a pad of sand (top layer) and Celite (bottom layer). The filtrate was separated and the organic layer was washed with brine (5 x 10 mL), dried over Na₂SO₄, and concentrated to give 1-(2-(aminomethyl)phenyl)-5-furyl-3-trifluoromethylpyrazole (1.4 g, 91.5%). ¹H NMR (CD₃OD) δ 7.69-7.61 (m, 2H), 7.52 (d, J = 1.5 Hz, 1H), 7.47 (td, J = 7.7 Hz, J = 1.1 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.07 (s, 1H), 6.34 (dd, J = 1.8 Hz, J = 3.6 Hz, 1H), 5.75 (d, J = 3.3 Hz, 1H), 3.40 (s, 2H); ESMS(+): 308 (M+H, 100);

35 To a solution of 1-(2-(aminomethyl)phenyl)-5-furyl-3-trifluoromethylpyrazole (1.4 g, 4.27 mmol) in THF (10 mL) was added a solution of (Boc)₂O (1.4 g, 6.4 mmol) in THF (10 mL), and the resulting mixture was stirred at room temperature for

1 hour. The mixture was diluted with EtOAc (100 mL), washed with water and brine, dried over Na₂SO₄, and concentrated to provide crude 1-(2-(*N*-Boc-aminomethyl)phenyl)-5-furyl-3-trifluoromethylpyrazole. ¹H NMR (CDCl₃) δ 7.60-7.55 (m, 2H),
5 7.42 (d, *J* = 6.2 Hz, 1H), 7.40 (s, 1H), 7.32 (d, *J* = 7.7 Hz, 1H), 6.95 (s, 1H), 6.28 (dd, *J* = 1.8 Hz, *J* = 3.3 Hz, 1H), 5.65 (d, *J* = 3.3 Hz, 1H), 4.01 (d, *J* = 6.8 Hz, 2H), 3.40 (s, 2H), 1.41 (s, 9H); ¹⁹F NMR (CDCl₃): δ -62.76.

To a solution of crude product in acetone (20 mL) and
10 water (20 mL) was portion by portion added KMnO₄ (3.95 g, 25 mmol), and the resulting mixture was stirred at 60 °C for 20 minutes and then filtered through Celite. The filtrate was concentrated, acidified with 1N HCl to pH 4, and extracted with EtOAc (3 x 50 mL). The organic layer was washed with
15 brine, dried over Na₂SO₄, concentrated, and purified by column chromatography with 20% MeOH in dichloromethane to provide 1-(2-(*N*-Boc-aminomethyl)phenyl)-3-trifluoromethylpyrazol-5-yl-carboxylic acid (1.05 g, 56% for the two steps). ESMS(-): 384.2 (M-H, 100).

20

Part D: 1-(2-(*N*-Boc-aminomethyl)phenyl)-3-trifluoromethyl-5-
[[(2-fluoro)-(2'-hydroxymethylsilyloxymethyl)-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole: To a solution of 1-(2-(*N*-Boc-aminomethyl)phenyl)-3-trifluoromethylpyrazol-5-yl-carboxylic
25 acid (0.768 g, 2 mmol) in CH₂Cl₂ (50 mL) was added DMF (1 drop) and oxalyl chloride (0.381 g, 3 mmol), and the resulting mixture was stirred at room temperature for 1.5 hours. The mixture was concentrated and the residue was dissolved in THF (10 mL). To the solution was added a solution of 2-fluoro-4-
30 (2'-(*tert*-butyldimethylsilyloxymethyl)phenyl)aniline (0.6 g, 1.8 mmol) in THF (10 mL) and Et₃N (1.5 mL), and the resulting mixture was stirred at room temperature for 24 hours. The mixture was diluted with EtOAc (100 mL), washed with water and brine, dried over MgSO₄, and purified on thin layer
35 chromatography with CH₂Cl₂/hexane (3:2) to give 1-(2-(*N*-Boc-aminomethyl)phenyl)-3-trifluoromethyl-5-[[[(2-fluoro)-(2'-*tert*-butyldimethylsilyloxymethyl)-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole (0.49 g, 80%).

To a solution of 1-(2'-N-Boc-aminomethylphenyl)-3-trifluoromethyl-5-(((2-fluoro)-(2'-tert-butyl)dimethylsilyloxymethyl)-[1,1']-biphen-4-yl)aminocarbonylpyrazole (0.57 g, 0.93 mmol) in THF (10 mL) was added Bu₄NF (1M in THF, 3 mL), and the resulting solution was stirred at room temperature for 2 hours. The mixture was diluted with EtOAc (150 mL), washed with water (20 mL), dried over Na₂SO₄, and purified by column chromatography with a gradient solvent (hexane to EtOAc) to give 1-(2-(N-Boc-aminomethyl)phenyl)-3-trifluoromethyl-5-(((2-fluoro)-(2'-hydroxymethyl)-[1,1']-biphen-4-yl)aminocarbonyl)pyrazole (484 mg, ~ 100%). ¹H NMR (CD₃OD) δ 7.69 (t, J = 8.0 Hz, 1H), 7.55-7.27 (m, 9H), 7.21 (dd, J = 7.4 Hz, J = 1.8 Hz, 1H), 7.13 (dd, J = 8.4 Hz, J = 1.1 Hz, 1H), 4.46 (s, 2H), 4.05 (s, 2H), 1.34 (s, 9H); ¹⁹F NMR (CD₃OD): δ -64.08, -125.53; ESMS(+): 606.3 (M+Na, 100).

Part E: 1-(2-(aminomethyl)phenyl)-3-trifluoromethyl-5-(((2-fluoro)-(2'-pyrrolidinomethyl)-[1,1']-biphen-4-yl)aminocarbonyl)pyrazole, TFA salt: To a solution of 1-(2-(N-Boc-aminomethyl)phenyl)-3-trifluoromethyl-5-(((2-fluoro)-(2'-hydroxymethyl)-[1,1']-biphen-4-yl)aminocarbonyl)pyrazole (150 mg, 0.26 mmol) in THF (5 mL) was added Cs₂CO₃ (167 mg, 0.51 mmol) and MsCl (4 mg, 0.39 mmol). After the resulting mixture was stirred at room temperature for 18 hours and concentrated, the residue was dissolved in THF (10 mL) and treated with pyrrolidine (0.5 mL) at room temperature 8 hours. ESMS(+): 638.4 (M+H, 100). The mixture was treated with TFA/CH₂Cl₂ (1 to 1, 10 mL) at room temperature for 5 hours, and concentrated. The residue was purified on HPLC with a gradient solvent (H₂O-CH₃CN-0.05% TFA) on C18 give the title compound (50 mg, 36% for the two steps). ¹H NMR (CD₃OD) δ 7.80 (T, J = 8.1 Hz, 1H), 7.71-7.30 (m, 9H), 7.27 (dd, J = 11.3 Hz, J = 1.8 Hz, 1H), 7.15 (d, J = 8.4 Hz, 1H), 4.40 (s, 2H), 3.99 (s, 2H), 3.42-3.34 (m, 2H), 2.93-2.87 (m, 2H), 2.00-1.94 (m, 4H); ¹⁹F NMR (CD₃OD): δ -64.22, -77.57(TFA), -123.82; HRMS: 538.2243 for C₂₉H₂₈O₁F₄N₅.

Example 46

1-[2-(Aminomethyl)phenyl]-3-trifluoromethyl-5-[(2-fluoro)-(2'-hydroxymethyl)-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole•TFA

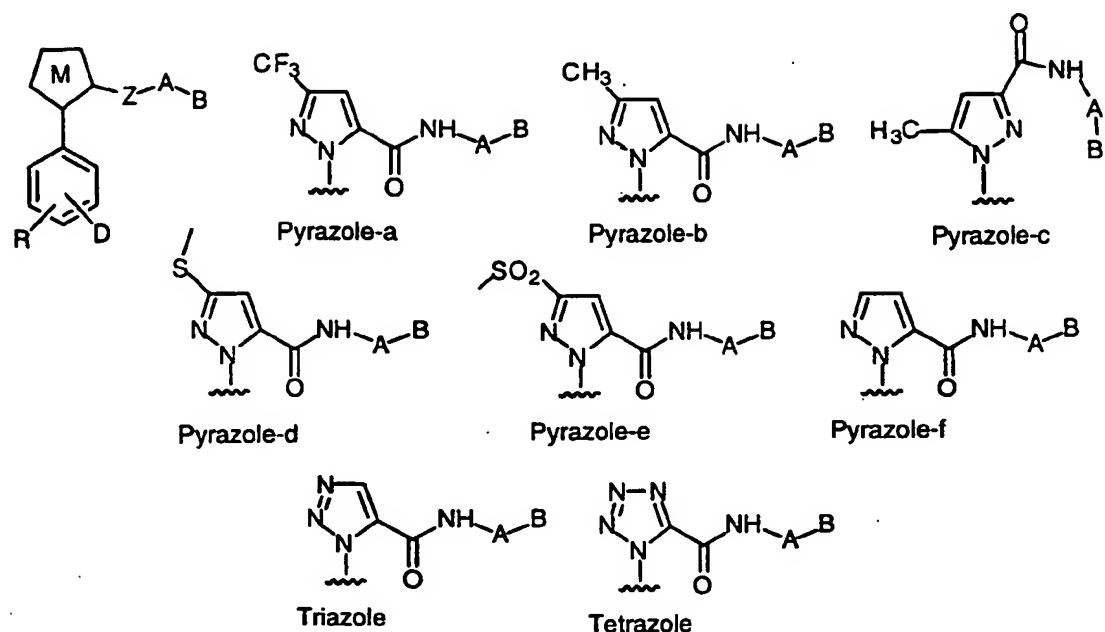
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A solution of 1-(2-(N-Boc-aminomethyl)phenyl)-3-trifluoromethyl-5-[(2-fluoro)-(2'-hydroxymethylsilyloxymethyl)-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole (10 mg) was treated with TFA/CH₂Cl₂ (1 to 1, 1 mL) at room temperature for 3 hours and concentrated. The residue was purified by HPLC with a gradient solvent (H₂O-CH₃CN-0.05% TFA) on C18 to give the title compound (2 mg). ¹H NMR (CD₃OD): δ 7.66-7.45 (m, 6H), 7.38-7.21 (m, 4H), 7.15 (d, J = 9.5 Hz, 1H), 7.10 (d, J = 6.6 Hz, 1H), 4.39 (s, 2H), 3.91 (s, 2H); ¹⁹F NMR (CD₃OD): δ -64.23, -77.38, -125.40; ESMS(-): 483.2 (M-H, 100).

10

15

Table 1



5 Unless otherwise indicated, D is at the 2-position and is CH_2NH_2 .

| Ex | M | A-B | MS |
|----|----------------------------------------------------------------------------------|---------------------------------------------------------|-------|
| 1 | pyrazole-b (R=4-OCH ₃) | 2'-H ₂ NSO ₂ -biphenyl | 492.2 |
| 2 | pyrazole-c (R=4-OCH ₃) | 2'-H ₂ NSO ₂ -biphenyl | 492.2 |
| 3 | pyrazole-b (D=CH ₂ N(Me) ₂) (R=4-OCH ₃) | 2'-(CH ₃)HNSO ₂ -biphenyl | 512 |
| 4 | pyrazole-a (R=4-OCH ₃) | 3-F-2'-H ₂ NSO ₂ -biphenyl | 528.1 |
| 5 | pyrazole-a (R=4-OCH ₃) | 3-F-2'-CH ₃ SO ₂ -biphenyl | 378.2 |
| 6 | pyrazole-a (R=4-OCH ₃) | 2'-CH ₃ SO ₂ -biphenyl | 545.1 |
| 7 | pyrazole-a (R=4-OCH ₃) | 2'-H ₂ NSO ₂ -biphenyl | 546.2 |
| 8 | pyrazole-a (R=4-OCH ₃) | 4-(N-pyrrolidino- carbonyl)phenyl | 488.2 |
| 9 | pyrazole-a (R=4-OCH ₃) | phenylmethylsulfonyl- piperidin-4-yl | 552.2 |
| 10 | pyrazole-a (R=4-OCH ₃) | 5-(2-H ₂ NSO ₂ -phenyl)pyrid-2-yl | 547.1 |
| 11 | pyrazole-a (R=4-OCH ₃) | 5-(2-pyridyl)pyrid-2-yl | 469.2 |
| 12 | pyrazole-a (R=4-OCH ₃) | benzylpiperidin-4-yl | 488.2 |
| 13 | pyrazole-a (R=4-OCH ₃) | phenylsulfonylpiperidin-4-yl | 538.2 |

| | | | |
|----|--------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|-------|
| 14 | pyrazole-a (R=4-Cl) | 3-F-2'-CH ₃ SO ₂ -biphenyl | 567.1 |
| 15 | pyrazole-a (R=4-Cl) | 3-F-2'-H ₂ NSO ₂ -biphenyl | 568.1 |
| 16 | pyrazole-a (R=5-Cl) | 3-F-2'-CH ₃ SO ₂ -biphenyl | 567.1 |
| 17 | pyrazole-a (R=5-Cl) | 3-F-2'-H ₂ NSO ₂ -biphenyl | 568.1 |
| 18 | pyrazole-a (R=4-F) | 3-F-2'-CH ₃ SO ₂ -biphenyl | 551.1 |
| 19 | pyrazole-a (R=4-F) | 3-F-2'-H ₂ NSO ₂ -biphenyl | 552.1 |
| 20 | pyrazole-a (R=5-F) | 3-F-2'-CH ₃ SO ₂ -biphenyl | 551.1 |
| 21 | pyrazole-a (R=5-F) | 3-F-2'-H ₂ NSO ₂ -biphenyl | 552.1 |
| 22 | pyrazole-a (R=4,5-F) | 3-F-2'-CH ₃ SO ₂ -biphenyl | 569.1 |
| 23 | pyrazole-a (R=4,5-F) | 3-F-2'-H ₂ NSO ₂ -biphenyl | 570.1 |
| 24 | pyrazole-a (R=3-F) | 3-F-2'-CH ₃ SO ₂ -biphenyl | 551.1 |
| 25 | pyrazole-a (R=3-F) | 3-F-2'-H ₂ NSO ₂ -biphenyl | 552.1 |
| 26 | pyrazole-a (R=4-F) | 2'-CH ₃ SO ₂ -biphenyl | 533.1 |
| 27 | pyrazole-a (R=4-F) | 2'-H ₂ NSO ₂ -biphenyl | 534.1 |
| 28 | pyrazole-a (R=4-F) | 4-(N-pyrrolidino-CH ₃ SO ₂ - iminolyl)phenyl | 553.2 |
| 29 | pyrazole-a (D=N-glycyl- NH ₂ CH ₂) (R=4-OCH ₃) | 3-F-2'-CH ₃ SO ₂ -biphenyl | 620.2 |
| 30 | pyrazole-a (D=C ₆ H ₅ CH ₂ C(O)- NH ₂ CH ₂) (R=4-OCH ₃) | 3-F-2'-CH ₃ SO ₂ -biphenyl | 681.2 |
| 31 | pyrazole-a | 2'-CH ₃ SO ₂ -biphenyl | 515.1 |
| 32 | pyrazole-a | 2'-H ₂ NSO ₂ -biphenyl | 516.1 |
| 33 | pyrazole-a | 3-F-2'-H ₂ NSO ₂ -biphenyl | 534.1 |
| 34 | pyrazole-a | 3-F-2'-CH ₃ SO ₂ -biphenyl | 533.1 |
| 35 | pyrazole-a (D=glycyl-NH ₂ CH ₂) | 3-F-2'-CH ₃ SO ₂ -biphenyl | 590.1 |
| 36 | pyrazole-a (D=N-CH ₃ -glycyl- NH ₂ CH ₂) | 3-F-2'-CH ₃ SO ₂ -biphenyl | 604.2 |
| 37 | pyrazole-a (D=CONH ₂) | 3-F-2'-CH ₃ SO ₂ -biphenyl | |

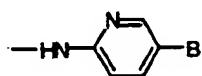
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|----|----------------------|--------------------------------------------------|-------|
| 38 | pyrazole-a (D=CN) | 3-F-2'-CH ₃ SO ₂ -biphenyl | |
| 39 | tetrazole | 3-F-2'-CH ₃ SO ₂ -biphenyl | 467 |
| 40 | tetrazole | 3-F-2'-H ₂ NSO ₂ -biphenyl | 468 |
| 41 | pyrazole-d | 3-F-2'-CH ₃ SO ₂ -biphenyl | 511.1 |
| 42 | pyrazole-e | 3-F-2'-CH ₃ SO ₂ -biphenyl | 543.2 |
| 43 | triazole | 3-F-2'-CH ₃ SO ₂ -biphenyl | 466.2 |
| 44 | pyrazole-f | 3-F-2'-CH ₃ SO ₂ -biphenyl | 465.2 |

The following tables contain representative examples of the present invention. Each entry in each table is intended to be paired with each formulae at the start of the table.

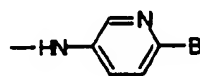
- 5 For example, in Table 2, example 1 is intended to be paired with each of formulae a-bbbb and in Table 3, example 1 is intended to be paired with each of formulae a-bbbb.

The following groups are intended for group A in the following tables.

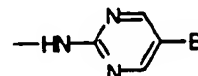
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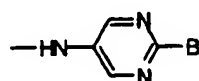
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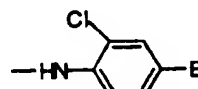
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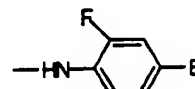
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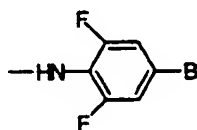
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2-Cl-phenyl

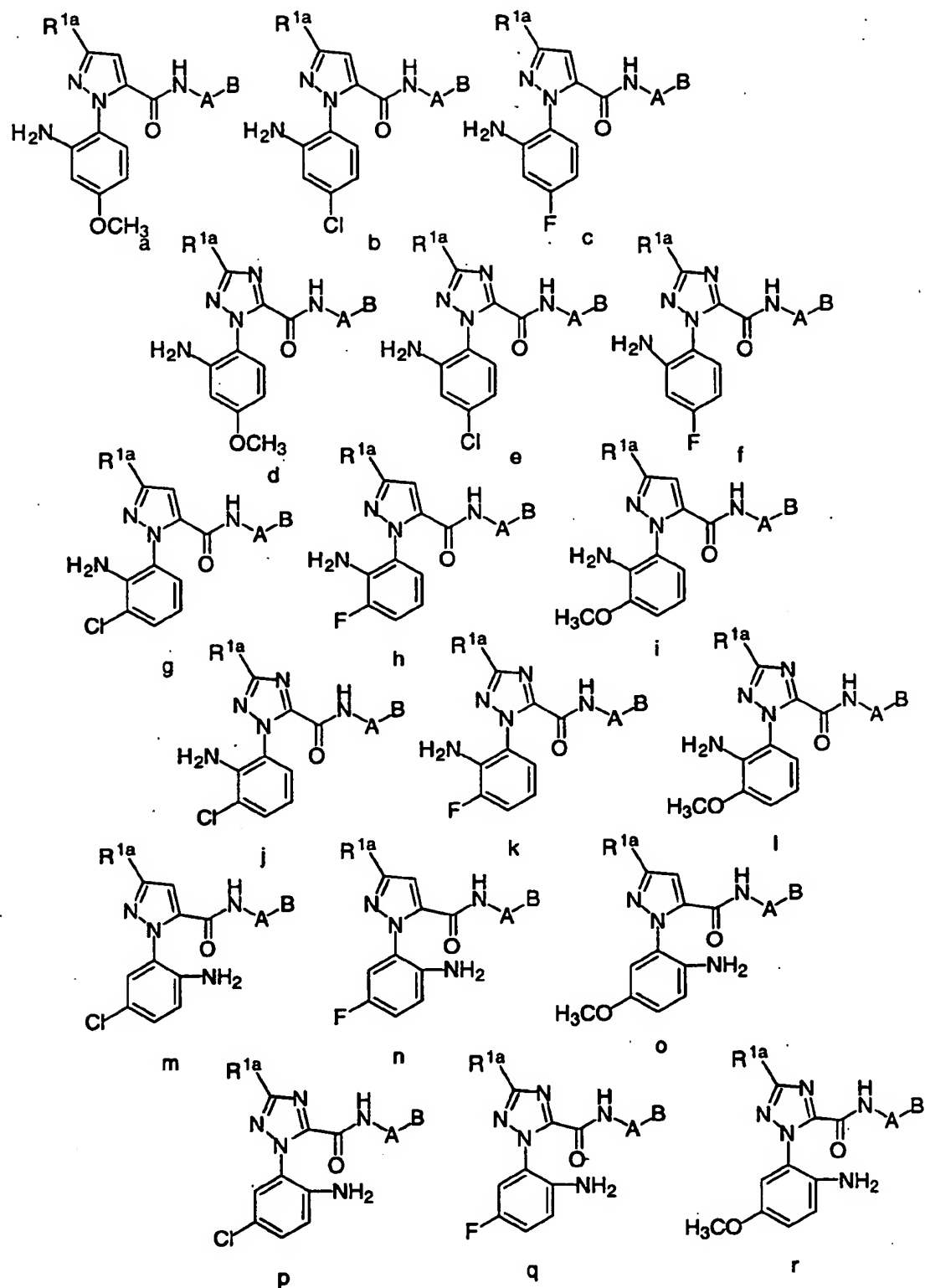


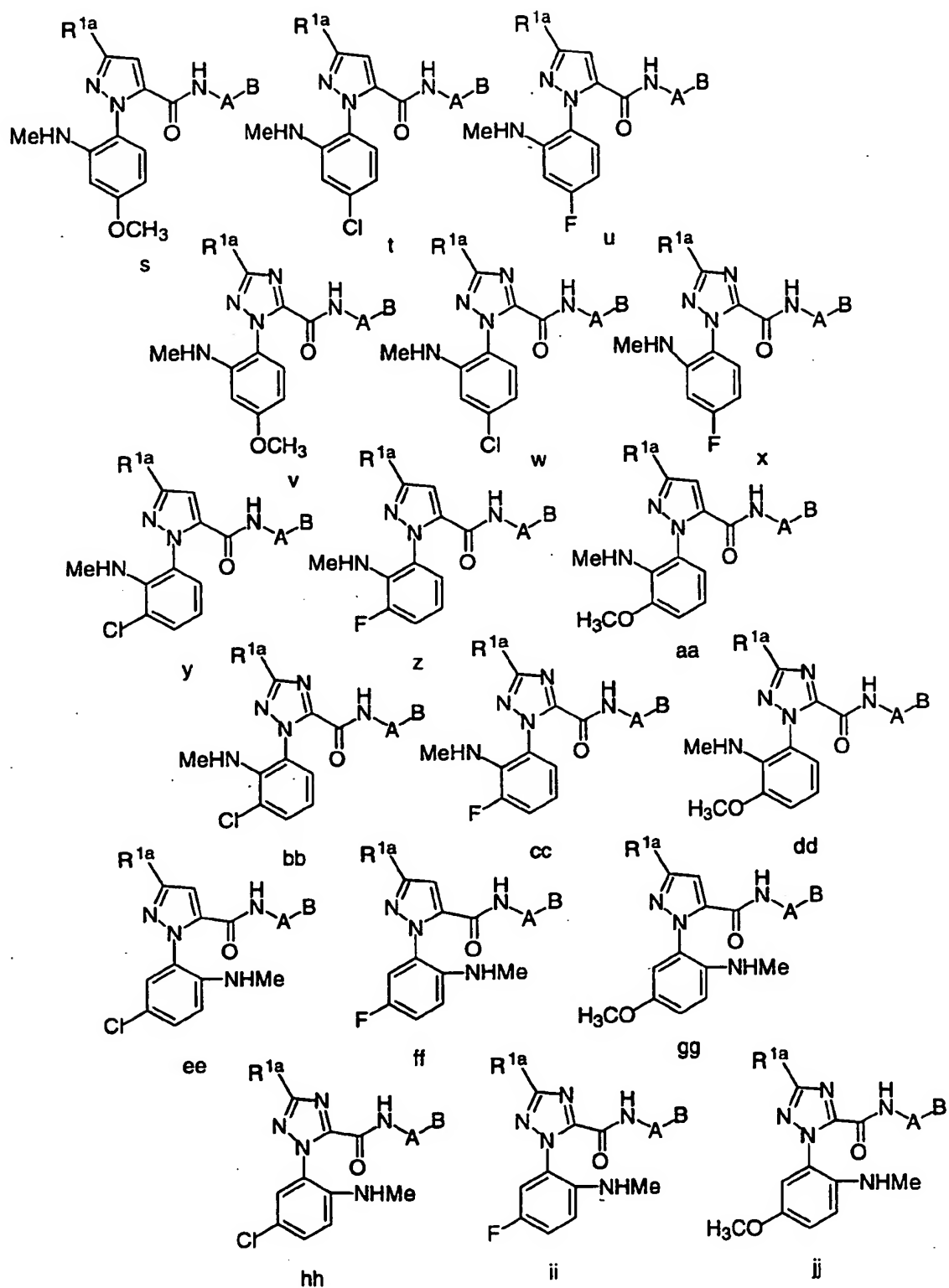
2-F-phenyl

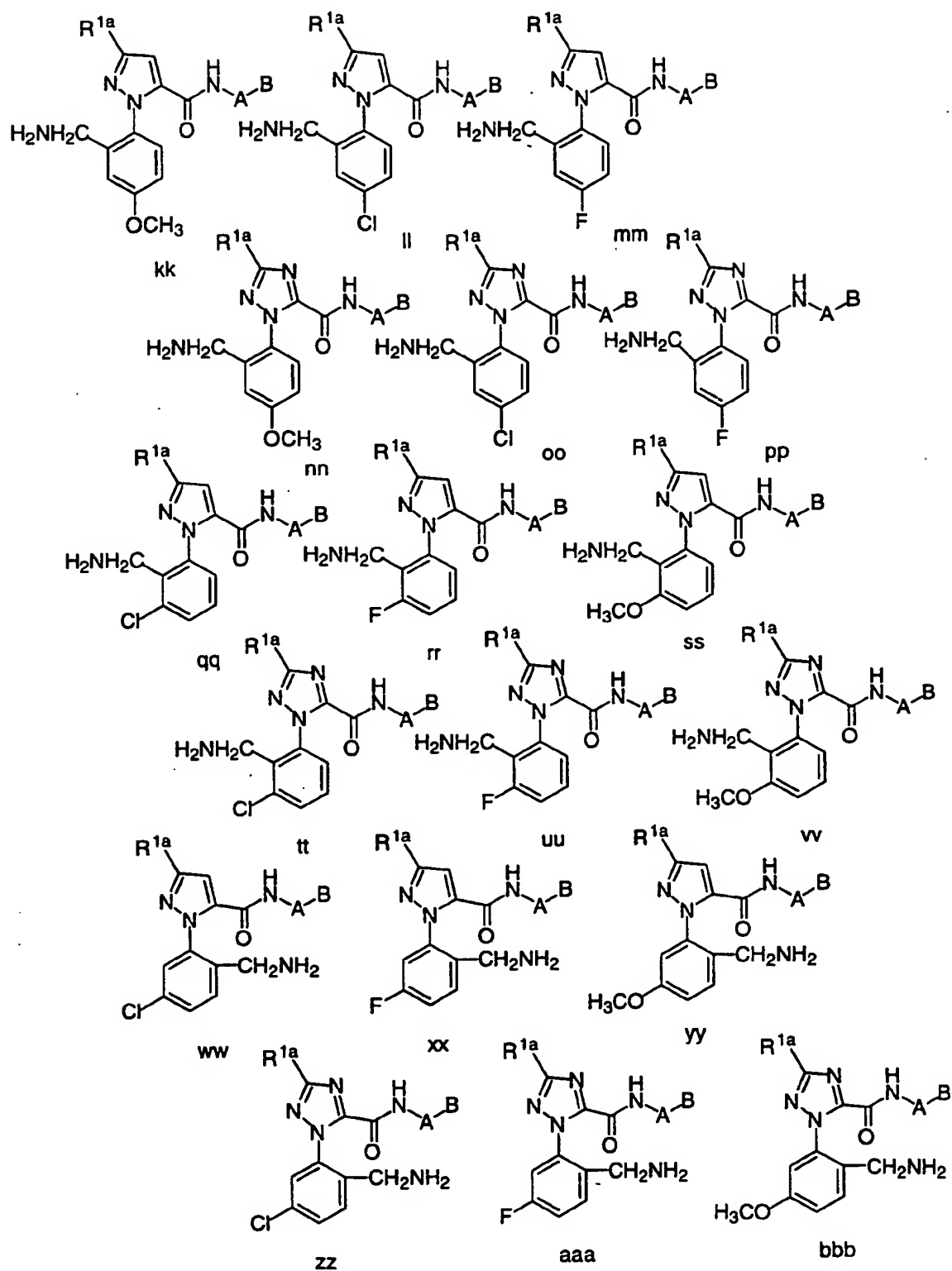


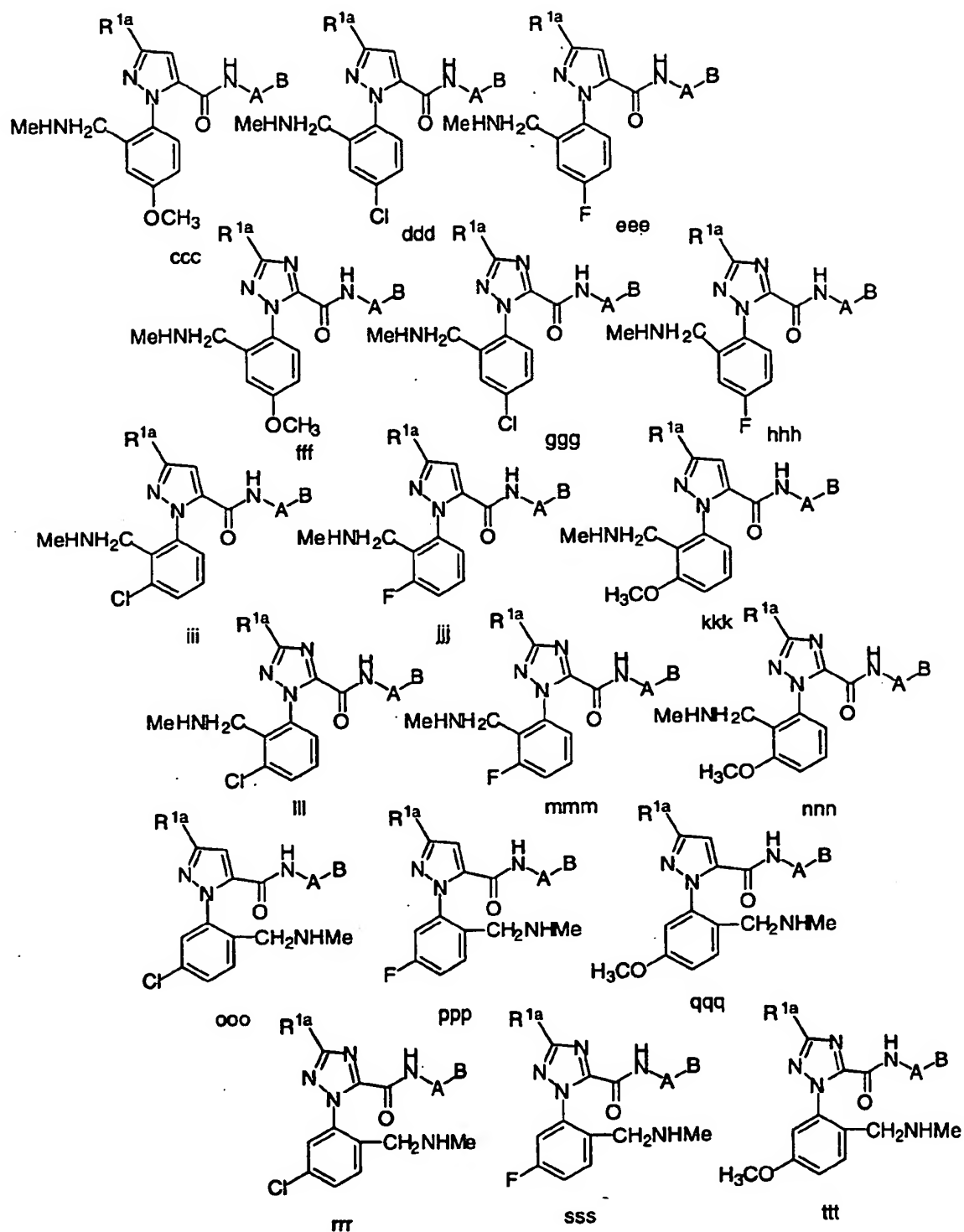
2,6-diF-phenyl

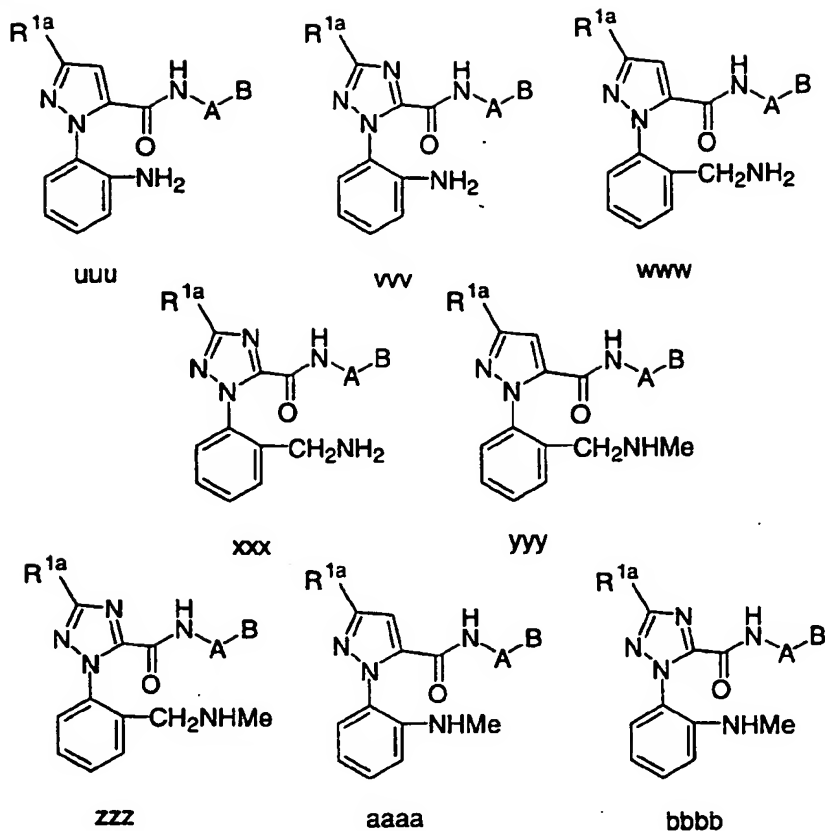
Table 2











| | Ex # | R^{1a} | A | B |
|----|------|-----------------|-----------|---------------------------------------------|
| 5 | 1 | CH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| | 2 | CH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 3 | CH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 4 | CH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 5 | CH ₃ | phenyl | 4-morpholino |
| 10 | 6 | CH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 7 | CH ₃ | phenyl | 4-morpholinocarbonyl |
| | 8 | CH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 9 | CH ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 10 | CH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| 15 | 11 | CH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 12 | CH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 13 | CH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 14 | CH ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 15 | CH ₃ | 2-pyridyl | 4-morpholino |
| 20 | 16 | CH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 17 | CH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| | 18 | CH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 19 | CH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 20 | CH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| 25 | 21 | CH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 22 | CH ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 23 | CH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |

| | | | | |
|----|----|-----------------|----------------|---------------------------------------------|
| | 24 | CH ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 25 | CH ₃ | 3-pyridyl | 4-morpholino |
| | 26 | CH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 27 | CH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| 5 | 28 | CH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 29 | CH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 30 | CH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 31 | CH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 32 | CH ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| 10 | 33 | CH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 34 | CH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 35 | CH ₃ | 2-pyrimidyl | 4-morpholino |
| | 36 | CH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 37 | CH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| 15 | 38 | CH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 39 | CH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 40 | CH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 41 | CH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 42 | CH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| 20 | 43 | CH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 44 | CH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 45 | CH ₃ | 5-pyrimidyl | 4-morpholino |
| | 46 | CH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 47 | CH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| 25 | 48 | CH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 49 | CH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 50 | CH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 51 | CH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 52 | CH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| 30 | 53 | CH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 54 | CH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 55 | CH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 56 | CH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 57 | CH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| 35 | 58 | CH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 59 | CH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 60 | CH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 61 | CH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 62 | CH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| 40 | 63 | CH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 64 | CH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 65 | CH ₃ | 2-F-phenyl | 4-morpholino |
| | 66 | CH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 67 | CH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| 45 | 68 | CH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 69 | CH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 70 | CH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 71 | CH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 72 | CH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| 50 | 73 | CH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 74 | CH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 75 | CH ₃ | 2,6-diF-phenyl | 4-morpholino |

| | | | | |
|----|-----|---------------------------------|----------------|---------------------------------------------|
| | 76 | CH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 77 | CH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 78 | CH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 79 | CH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| 5 | 80 | CH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 81 | CH ₂ CH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| | 82 | CH ₂ CH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 83 | CH ₂ CH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 84 | CH ₂ CH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| 10 | 85 | CH ₂ CH ₃ | phenyl | 4-morpholino |
| | 86 | CH ₂ CH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 87 | CH ₂ CH ₃ | phenyl | 4-morpholinocarbonyl |
| | 88 | CH ₂ CH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 89 | CH ₂ CH ₃ | phenyl | 5-methyl-1-imidazolyl |
| 15 | 90 | CH ₂ CH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 91 | CH ₂ CH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 92 | CH ₂ CH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 93 | CH ₂ CH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 94 | CH ₂ CH ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| 20 | 95 | CH ₂ CH ₃ | 2-pyridyl | 4-morpholino |
| | 96 | CH ₂ CH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 97 | CH ₂ CH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| | 98 | CH ₂ CH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 99 | CH ₂ CH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| 25 | 100 | CH ₂ CH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 101 | CH ₂ CH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 102 | CH ₂ CH ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 103 | CH ₂ CH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 104 | CH ₂ CH ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| 30 | 105 | CH ₂ CH ₃ | 3-pyridyl | 4-morpholino |
| | 106 | CH ₂ CH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 107 | CH ₂ CH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| | 108 | CH ₂ CH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 109 | CH ₂ CH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| 35 | 110 | CH ₂ CH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 111 | CH ₂ CH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 112 | CH ₂ CH ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 113 | CH ₂ CH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 114 | CH ₂ CH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 40 | 115 | CH ₂ CH ₃ | 2-pyrimidyl | 4-morpholino |
| | 116 | CH ₂ CH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 117 | CH ₂ CH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 118 | CH ₂ CH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 119 | CH ₂ CH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| 45 | 120 | CH ₂ CH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 121 | CH ₂ CH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 122 | CH ₂ CH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 123 | CH ₂ CH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 124 | CH ₂ CH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 50 | 125 | CH ₂ CH ₃ | 5-pyrimidyl | 4-morpholino |
| | 126 | CH ₂ CH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 127 | CH ₂ CH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |

| | | | | |
|----|-----|---------------------------------|----------------|---------------------------------------------|
| | 128 | CH ₂ CH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 129 | CH ₂ CH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 130 | CH ₂ CH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 131 | CH ₂ CH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| 5 | 132 | CH ₂ CH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 133 | CH ₂ CH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 134 | CH ₂ CH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 135 | CH ₂ CH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 136 | CH ₂ CH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 10 | 137 | CH ₂ CH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 138 | CH ₂ CH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 139 | CH ₂ CH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 140 | CH ₂ CH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 141 | CH ₂ CH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| 15 | 142 | CH ₂ CH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 143 | CH ₂ CH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 144 | CH ₂ CH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 145 | CH ₂ CH ₃ | 2-F-phenyl | 4-morpholino |
| | 146 | CH ₂ CH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 20 | 147 | CH ₂ CH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 148 | CH ₂ CH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 149 | CH ₂ CH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 150 | CH ₂ CH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 151 | CH ₂ CH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| 25 | 152 | CH ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 153 | CH ₂ CH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 154 | CH ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 155 | CH ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 156 | CH ₂ CH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 30 | 157 | CH ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 158 | CH ₂ CH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 159 | CH ₂ CH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 160 | CH ₂ CH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 161 | CF ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| 35 | 162 | CF ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 163 | CF ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 164 | CF ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 165 | CF ₃ | phenyl | 4-morpholino |
| | 166 | CF ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 40 | 167 | CF ₃ | phenyl | 4-morpholinocarbonyl |
| | 168 | CF ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 169 | CF ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 170 | CF ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 171 | CF ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| 45 | 172 | CF ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 173 | CF ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 174 | CF ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 175 | CF ₃ | 2-pyridyl | 4-morpholino |
| | 176 | CF ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 50 | 177 | CF ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| | 178 | CF ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 179 | CF ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |

| | | | | |
|----|-----|-----------------|----------------|---------------------------------------------|
| | 180 | CF ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 181 | CF ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 182 | CF ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 183 | CF ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| 5 | 184 | CF ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 185 | CF ₃ | 3-pyridyl | 4-morpholino |
| | 186 | CF ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 187 | CF ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| | 188 | CF ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| 10 | 189 | CF ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 190 | CF ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 191 | CF ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 192 | CF ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 193 | CF ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| 15 | 194 | CF ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 195 | CF ₃ | 2-pyrimidyl | 4-morpholino |
| | 196 | CF ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 197 | CF ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 198 | CF ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| 20 | 199 | CF ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 200 | CF ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 201 | CF ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 202 | CF ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 203 | CF ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| 25 | 204 | CF ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 205 | CF ₃ | 5-pyrimidyl | 4-morpholino |
| | 206 | CF ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 207 | CF ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 208 | CF ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| 30 | 209 | CF ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 210 | CF ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 211 | CF ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 212 | CF ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 213 | CF ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| 35 | 214 | CF ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 215 | CF ₃ | 2-Cl-phenyl | 4-morpholino |
| | 216 | CF ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 217 | CF ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 218 | CF ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| 40 | 219 | CF ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 220 | CF ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 221 | CF ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 222 | CF ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 223 | CF ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| 45 | 224 | CF ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 225 | CF ₃ | 2-F-phenyl | 4-morpholino |
| | 226 | CF ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 227 | CF ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 228 | CF ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| 50 | 229 | CF ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 230 | CF ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 231 | CF ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |

| | | | | |
|----|-----|------------------|----------------|---------------------------------------------|
| | 232 | CF ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 233 | CF ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 234 | CF ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 235 | CF ₃ | 2,6-diF-phenyl | 4-morpholino |
| 5 | 236 | CF ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 237 | CF ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 238 | CF ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 239 | CF ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 240 | CF ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 10 | 241 | SCH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| | 242 | SCH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 243 | SCH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 244 | SCH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 245 | SCH ₃ | phenyl | 4-morpholino |
| 15 | 246 | SCH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 247 | SCH ₃ | phenyl | 4-morpholinocarbonyl |
| | 248 | SCH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 249 | SCH ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 250 | SCH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| 20 | 251 | SCH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 252 | SCH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 253 | SCH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 254 | SCH ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 255 | SCH ₃ | 2-pyridyl | 4-morpholino |
| 25 | 256 | SCH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 257 | SCH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| | 258 | SCH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 259 | SCH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 260 | SCH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| 30 | 261 | SCH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 262 | SCH ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 263 | SCH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 264 | SCH ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 265 | SCH ₃ | 3-pyridyl | 4-morpholino |
| 35 | 266 | SCH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 267 | SCH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| | 268 | SCH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 269 | SCH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 270 | SCH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| 40 | 271 | SCH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 272 | SCH ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 273 | SCH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 274 | SCH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 275 | SCH ₃ | 2-pyrimidyl | 4-morpholino |
| 45 | 276 | SCH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 277 | SCH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 278 | SCH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 279 | SCH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 280 | SCH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| 50 | 281 | SCH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 282 | SCH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 283 | SCH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |

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|----|-----|-------------------|----------------|---------------------------------------------|
| | 284 | SCH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 285 | SCH ₃ | 5-pyrimidyl | 4-morpholino |
| | 286 | SCH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 287 | SCH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| 5 | 288 | SCH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 289 | SCH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 290 | SCH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 291 | SCH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 292 | SCH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| 10 | 293 | SCH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 294 | SCH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 295 | SCH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 296 | SCH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 297 | SCH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| 15 | 298 | SCH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 299 | SCH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 300 | SCH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 301 | SCH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 302 | SCH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| 20 | 303 | SCH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 304 | SCH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 305 | SCH ₃ | 2-F-phenyl | 4-morpholino |
| | 306 | SCH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 307 | SCH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| 25 | 308 | SCH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 309 | SCH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 310 | SCH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 311 | SCH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 312 | SCH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| 30 | 313 | SCH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 314 | SCH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 315 | SCH ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 316 | SCH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 317 | SCH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| 35 | 318 | SCH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 319 | SCH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 320 | SCH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 321 | SOCH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| | 322 | SOCH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| 40 | 323 | SOCH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 324 | SOCH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 325 | SOCH ₃ | phenyl | 4-morpholino |
| | 326 | SOCH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 327 | SOCH ₃ | phenyl | 4-morpholinocarbonyl |
| 45 | 328 | SOCH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 329 | SOCH ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 330 | SOCH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 331 | SOCH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 332 | SOCH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| 50 | 333 | SOCH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 334 | SOCH ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 335 | SOCH ₃ | 2-pyridyl | 4-morpholino |

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|----|-----|-------------------|-------------|---------------------------------------------|
| | 336 | SOCH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 337 | SOCH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| | 338 | SOCH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 339 | SOCH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| 5 | 340 | SOCH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 341 | SOCH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 342 | SOCH ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 343 | SOCH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 344 | SOCH ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| 10 | 345 | SOCH ₃ | 3-pyridyl | 4-morpholino |
| | 346 | SOCH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 347 | SOCH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| | 348 | SOCH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 349 | SOCH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| 15 | 350 | SOCH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 351 | SOCH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 352 | SOCH ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 353 | SOCH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 354 | SOCH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 20 | 355 | SOCH ₃ | 2-pyrimidyl | 4-morpholino |
| | 356 | SOCH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 357 | SOCH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 358 | SOCH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 359 | SOCH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| 25 | 360 | SOCH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 361 | SOCH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 362 | SOCH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 363 | SOCH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 364 | SOCH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 30 | 365 | SOCH ₃ | 5-pyrimidyl | 4-morpholino |
| | 366 | SOCH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 367 | SOCH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 368 | SOCH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 369 | SOCH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| 35 | 370 | SOCH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 371 | SOCH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 372 | SOCH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 373 | SOCH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 374 | SOCH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| 40 | 375 | SOCH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 376 | SOCH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 377 | SOCH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 378 | SOCH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 379 | SOCH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| 45 | 380 | SOCH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 381 | SOCH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 382 | SOCH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 383 | SOCH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 384 | SOCH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| 50 | 385 | SOCH ₃ | 2-F-phenyl | 4-morpholino |
| | 386 | SOCH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 387 | SOCH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |

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|----|-----|---------------------------------|----------------|---------------------------------------------|
| | 388 | SOCH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 389 | SOCH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 390 | SOCH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 391 | SOCH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| 5 | 392 | SOCH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 393 | SOCH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 394 | SOCH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 395 | SOCH ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 396 | SOCH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 10 | 397 | SOCH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 398 | SOCH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 399 | SOCH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 400 | SOCH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 401 | SO ₂ CH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| 15 | 402 | SO ₂ CH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 403 | SO ₂ CH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 404 | SO ₂ CH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 405 | SO ₂ CH ₃ | phenyl | 4-morpholino |
| | 406 | SO ₂ CH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 20 | 407 | SO ₂ CH ₃ | phenyl | 4-morpholinocarbonyl |
| | 408 | SO ₂ CH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 409 | SO ₂ CH ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 410 | SO ₂ CH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 411 | SO ₂ CH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| 25 | 412 | SO ₂ CH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 413 | SO ₂ CH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 414 | SO ₂ CH ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 415 | SO ₂ CH ₃ | 2-pyridyl | 4-morpholino |
| | 416 | SO ₂ CH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 30 | 417 | SO ₂ CH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| | 418 | SO ₂ CH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 419 | SO ₂ CH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 420 | SO ₂ CH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 421 | SO ₂ CH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| 35 | 422 | SO ₂ CH ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 423 | SO ₂ CH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 424 | SO ₂ CH ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 425 | SO ₂ CH ₃ | 3-pyridyl | 4-morpholino |
| | 426 | SO ₂ CH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 40 | 427 | SO ₂ CH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| | 428 | SO ₂ CH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 429 | SO ₂ CH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 430 | SO ₂ CH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 431 | SO ₂ CH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 45 | 432 | SO ₂ CH ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 433 | SO ₂ CH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 434 | SO ₂ CH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 435 | SO ₂ CH ₃ | 2-pyrimidyl | 4-morpholino |
| | 436 | SO ₂ CH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 50 | 437 | SO ₂ CH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 438 | SO ₂ CH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 439 | SO ₂ CH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |

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| | 440 | SO ₂ CH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 441 | SO ₂ CH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 442 | SO ₂ CH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 443 | SO ₂ CH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| 5 | 444 | SO ₂ CH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 445 | SO ₂ CH ₃ | 5-pyrimidyl | 4-morpholino |
| | 446 | SO ₂ CH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 447 | SO ₂ CH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 448 | SO ₂ CH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| 10 | 449 | SO ₂ CH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 450 | SO ₂ CH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 451 | SO ₂ CH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 452 | SO ₂ CH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 453 | SO ₂ CH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| 15 | 454 | SO ₂ CH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 455 | SO ₂ CH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 456 | SO ₂ CH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 457 | SO ₂ CH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 458 | SO ₂ CH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| 20 | 459 | SO ₂ CH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 460 | SO ₂ CH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 461 | SO ₂ CH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 462 | SO ₂ CH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 463 | SO ₂ CH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| 25 | 464 | SO ₂ CH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 465 | SO ₂ CH ₃ | 2-F-phenyl | 4-morpholino |
| | 466 | SO ₂ CH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 467 | SO ₂ CH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 468 | SO ₂ CH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| 30 | 469 | SO ₂ CH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 470 | SO ₂ CH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 471 | SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 472 | SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 473 | SO ₂ CH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| 35 | 474 | SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 475 | SO ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 476 | SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 477 | SO ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 478 | SO ₂ CH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| 40 | 479 | SO ₂ CH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 480 | SO ₂ CH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 481 | CH ₂ NH | phenyl | 2-(aminosulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 482 | CH ₂ NH | phenyl | 2-(methylaminosulfonyl)phenyl |
| 45 | | -SO ₂ CH ₃ | | |
| | 483 | CH ₂ NH | phenyl | 1-pyrrolidinocarbonyl |
| | | -SO ₂ CH ₃ | | |
| | 484 | CH ₂ NH | phenyl | 2-(methylsulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |
| 50 | 485 | CH ₂ NH | phenyl | 4-morpholino |
| | | -SO ₂ CH ₃ | | |
| | 486 | CH ₂ NH | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |

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|----|-----|----------------------------------|-------------|---------------------------------------------|
| | | -SO ₂ CH ₃ | | |
| | 487 | CH ₂ NH | phenyl | 4-morpholinocarbonyl |
| | | -SO ₂ CH ₃ | | |
| | 488 | CH ₂ NH | phenyl | 2-methyl-1-imidazolyl |
| 5 | | -SO ₂ CH ₃ | | |
| | 489 | CH ₂ NH | phenyl | 5-methyl-1-imidazolyl |
| | | -SO ₂ CH ₃ | | |
| | 490 | CH ₂ NH | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | | -SO ₂ CH ₃ | | |
| 10 | 491 | CH ₂ NH | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 492 | CH ₂ NH | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 493 | CH ₂ NH | 2-pyridyl | 1-pyrrolidinocarbonyl |
| 15 | | -SO ₂ CH ₃ | | |
| | 494 | CH ₂ NH | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 495 | CH ₂ NH | 2-pyridyl | 4-morpholino |
| | | -SO ₂ CH ₃ | | |
| 20 | 496 | CH ₂ NH | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 497 | CH ₂ NH | 2-pyridyl | 4-morpholinocarbonyl |
| | | -SO ₂ CH ₃ | | |
| | 498 | CH ₂ NH | 2-pyridyl | 2-methyl-1-imidazolyl |
| 25 | | -SO ₂ CH ₃ | | |
| | 499 | CH ₂ NH | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 500 | CH ₂ NH | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | | -SO ₂ CH ₃ | | |
| | 501 | CH ₂ NH | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| 30 | | -SO ₂ CH ₃ | | |
| | 502 | CH ₂ NH | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 503 | CH ₂ NH | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | | -SO ₂ CH ₃ | | |
| 35 | 504 | CH ₂ NH | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 505 | CH ₂ NH | 3-pyridyl | 4-morpholino |
| | | -SO ₂ CH ₃ | | |
| | 506 | CH ₂ NH | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 40 | | -SO ₂ CH ₃ | | |
| | 507 | CH ₂ NH | 3-pyridyl | 4-morpholinocarbonyl |
| | | -SO ₂ CH ₃ | | |
| | 508 | CH ₂ NH | 3-pyridyl | 2-methyl-1-imidazolyl |
| | | -SO ₂ CH ₃ | | |
| 45 | 509 | CH ₂ NH | 3-pyridyl | 5-methyl-1-imidazolyl |
| | | -SO ₂ CH ₃ | | |
| | 510 | CH ₂ NH | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | | -SO ₂ CH ₃ | | |
| | 511 | CH ₂ NH | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 50 | | -SO ₂ CH ₃ | | |
| | 512 | CH ₂ NH | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |

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|----|-----|--------------------------------------------------------|-------------|---------------------------------------------|
| | 513 | CH ₂ NH -SO ₂ CH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 514 | CH ₂ NH -SO ₂ CH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 5 | 515 | CH ₂ NH -SO ₂ CH ₃ | 2-pyrimidyl | 4-morpholino |
| | 516 | CH ₂ NH -SO ₂ CH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 10 | 517 | CH ₂ NH -SO ₂ CH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 518 | CH ₂ NH -SO ₂ CH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 519 | CH ₂ NH -SO ₂ CH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| 15 | 520 | CH ₂ NH -SO ₂ CH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 521 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 20 | 522 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 523 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 524 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 25 | 525 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 4-morpholino |
| | 526 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 30 | 527 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 528 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 529 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| 35 | 530 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 531 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| 40 | 532 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 533 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 534 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| 45 | 535 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 536 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 50 | 537 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 538 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |

| | | | | |
|----|-----|--------------------------------------------------------|----------------|---------------------------------------------|
| | 539 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 540 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 5 | 541 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 542 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 2-(methyaminosulfonyl)phenyl |
| | 543 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| 10 | 544 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 545 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 4-morpholino |
| 15 | 546 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 547 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 548 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| 20 | 549 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 550 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 25 | 551 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 552 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(methyaminosulfonyl)phenyl |
| | 553 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| 30 | 554 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 555 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholino |
| 35 | 556 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 557 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 558 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| 40 | 559 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 560 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 45 | 561 | Cl | phenyl | 2-(aminosulfonyl)phenyl |
| | 562 | Cl | phenyl | 2-(methyaminosulfonyl)phenyl |
| | 563 | Cl | phenyl | 1-pyrrolidinocarbonyl |
| | 564 | Cl | phenyl | 2-(methylsulfonyl)phenyl |
| | 565 | Cl | phenyl | 4-morpholino |
| 50 | 566 | Cl | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 567 | Cl | phenyl | 4-morpholinocarbonyl |
| | 568 | Cl | phenyl | 2-methyl-1-imidazolyl |
| | 569 | Cl | phenyl | 5-methyl-1-imidazolyl |

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|----|-----|----|-------------|---------------------------------------------|
| | 570 | Cl | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 571 | Cl | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 572 | Cl | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 573 | Cl | 2-pyridyl | 1-pyrrolidinocarbonyl |
| 5 | 574 | Cl | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 575 | Cl | 2-pyridyl | 4-morpholino |
| | 576 | Cl | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 577 | Cl | 2-pyridyl | 4-morpholinocarbonyl |
| | 578 | Cl | 2-pyridyl | 2-methyl-1-imidazolyl |
| 10 | 579 | Cl | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 580 | Cl | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 581 | Cl | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 582 | Cl | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 583 | Cl | 3-pyridyl | 1-pyrrolidinocarbonyl |
| 15 | 584 | Cl | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 585 | Cl | 3-pyridyl | 4-morpholino |
| | 586 | Cl | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 587 | Cl | 3-pyridyl | 4-morpholinocarbonyl |
| | 588 | Cl | 3-pyridyl | 2-methyl-1-imidazolyl |
| 20 | 589 | Cl | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 590 | Cl | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 591 | Cl | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 592 | Cl | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 593 | Cl | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| 25 | 594 | Cl | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 595 | Cl | 2-pyrimidyl | 4-morpholino |
| | 596 | Cl | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 597 | Cl | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 598 | Cl | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| 30 | 599 | Cl | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 600 | Cl | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 601 | Cl | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 602 | Cl | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 603 | Cl | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| 35 | 604 | Cl | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 605 | Cl | 5-pyrimidyl | 4-morpholino |
| | 606 | Cl | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 607 | Cl | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 608 | Cl | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| 40 | 609 | Cl | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 610 | Cl | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 611 | Cl | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 612 | Cl | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 613 | Cl | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| 45 | 614 | Cl | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 615 | Cl | 2-Cl-phenyl | 4-morpholino |
| | 616 | Cl | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 617 | Cl | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 618 | Cl | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| 50 | 619 | Cl | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 620 | Cl | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 621 | Cl | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 622 | Cl | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 623 | Cl | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| 55 | 624 | Cl | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 625 | Cl | 2-F-phenyl | 4-morpholino |

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|----|-----|----|----------------|---------------------------------------------|
| | 626 | Cl | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 627 | Cl | 2-F-phenyl | 4-morpholinocarbonyl |
| | 628 | Cl | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 629 | Cl | 2-F-phenyl | 5-methyl-1-imidazolyl |
| 5 | 630 | Cl | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 631 | Cl | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 632 | Cl | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 633 | Cl | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 634 | Cl | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| 10 | 635 | Cl | 2,6-diF-phenyl | 4-morpholino |
| | 636 | Cl | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 637 | Cl | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 638 | Cl | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 639 | Cl | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| 15 | 640 | Cl | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 641 | F | phenyl | 2-(aminosulfonyl)phenyl |
| | 642 | F | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 643 | F | phenyl | 1-pyrrolidinocarbonyl |
| | 644 | F | phenyl | 2-(methylsulfonyl)phenyl |
| 20 | 645 | F | phenyl | 4-morpholino |
| | 646 | F | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 647 | F | phenyl | 4-morpholinocarbonyl |
| | 648 | F | phenyl | 2-methyl-1-imidazolyl |
| | 649 | F | phenyl | 5-methyl-1-imidazolyl |
| 25 | 650 | F | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 651 | F | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 652 | F | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 653 | F | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 654 | F | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| 30 | 655 | F | 2-pyridyl | 4-morpholino |
| | 656 | F | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 657 | F | 2-pyridyl | 4-morpholinocarbonyl |
| | 658 | F | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 659 | F | 2-pyridyl | 5-methyl-1-imidazolyl |
| 35 | 660 | F | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 661 | F | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 662 | F | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 663 | F | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 664 | F | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| 40 | 665 | F | 3-pyridyl | 4-morpholino |
| | 666 | F | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 667 | F | 3-pyridyl | 4-morpholinocarbonyl |
| | 668 | F | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 669 | F | 3-pyridyl | 5-methyl-1-imidazolyl |
| 45 | 670 | F | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 671 | F | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 672 | F | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 673 | F | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 674 | F | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 50 | 675 | F | 2-pyrimidyl | 4-morpholino |
| | 676 | F | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 677 | F | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 678 | F | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 679 | F | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| 55 | 680 | F | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 681 | F | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |

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|----|-----|---------------------------------|----------------|---------------------------------------------|
| | 682 | F | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 683 | F | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 684 | F | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 685 | F | 5-pyrimidyl | 4-morpholino |
| 5 | 686 | F | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 687 | F | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 688 | F | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 689 | F | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 690 | F | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| 10 | 691 | F | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 692 | F | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 693 | F | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 694 | F | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 695 | F | 2-Cl-phenyl | 4-morpholino |
| 15 | 696 | F | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 697 | F | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 698 | F | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 699 | F | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 700 | F | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 20 | 701 | F | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 702 | F | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 703 | F | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 704 | F | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 705 | F | 2-F-phenyl | 4-morpholino |
| 25 | 706 | F | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 707 | F | 2-F-phenyl | 4-morpholinocarbonyl |
| | 708 | F | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 709 | F | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 710 | F | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 30 | 711 | F | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 712 | F | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 713 | F | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 714 | F | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 715 | F | 2,6-diF-phenyl | 4-morpholino |
| 35 | 716 | F | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 717 | F | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 718 | F | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 719 | F | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 720 | F | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 40 | 721 | CO ₂ CH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| | 722 | CO ₂ CH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 723 | CO ₂ CH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 724 | CO ₂ CH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 725 | CO ₂ CH ₃ | phenyl | 4-morpholino |
| 45 | 726 | CO ₂ CH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 727 | CO ₂ CH ₃ | phenyl | 4-morpholinocarbonyl |
| | 728 | CO ₂ CH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 729 | CO ₂ CH ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 730 | CO ₂ CH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| 50 | 731 | CO ₂ CH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 732 | CO ₂ CH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 733 | CO ₂ CH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 734 | CO ₂ CH ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 735 | CO ₂ CH ₃ | 2-pyridyl | 4-morpholino |
| 55 | 736 | CO ₂ CH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |

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|----|-----|---------------------------------|-------------|---------------------------------------------|
| | 737 | CO ₂ CH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| | 738 | CO ₂ CH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 739 | CO ₂ CH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 740 | CO ₂ CH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| 5 | 741 | CO ₂ CH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 742 | CO ₂ CH ₃ | 3-pyridyl | 2-(methylaninosulfonyl)phenyl |
| | 743 | CO ₂ CH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 744 | CO ₂ CH ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 745 | CO ₂ CH ₃ | 3-pyridyl | 4-morpholino |
| 10 | 746 | CO ₂ CH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 747 | CO ₂ CH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| | 748 | CO ₂ CH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 749 | CO ₂ CH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 750 | CO ₂ CH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| 15 | 751 | CO ₂ CH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 752 | CO ₂ CH ₃ | 2-pyrimidyl | 2-(methylaninosulfonyl)phenyl |
| | 753 | CO ₂ CH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 754 | CO ₂ CH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 755 | CO ₂ CH ₃ | 2-pyrimidyl | 4-morpholino |
| 20 | 756 | CO ₂ CH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 757 | CO ₂ CH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 758 | CO ₂ CH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 759 | CO ₂ CH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 760 | CO ₂ CH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| 25 | 761 | CO ₂ CH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 762 | CO ₂ CH ₃ | 5-pyrimidyl | 2-(methylaninosulfonyl)phenyl |
| | 763 | CO ₂ CH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 764 | CO ₂ CH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 765 | CO ₂ CH ₃ | 5-pyrimidyl | 4-morpholino |
| 30 | 766 | CO ₂ CH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 767 | CO ₂ CH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 768 | CO ₂ CH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 769 | CO ₂ CH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 770 | CO ₂ CH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| 35 | 771 | CO ₂ CH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 772 | CO ₂ CH ₃ | 2-Cl-phenyl | 2-(methylaninosulfonyl)phenyl |
| | 773 | CO ₂ CH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 774 | CO ₂ CH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 775 | CO ₂ CH ₃ | 2-Cl-phenyl | 4-morpholino |
| 40 | 776 | CO ₂ CH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 777 | CO ₂ CH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 778 | CO ₂ CH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 779 | CO ₂ CH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 780 | CO ₂ CH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 45 | 781 | CO ₂ CH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 782 | CO ₂ CH ₃ | 2-F-phenyl | 2-(methylaninosulfonyl)phenyl |
| | 783 | CO ₂ CH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 784 | CO ₂ CH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 785 | CO ₂ CH ₃ | 2-F-phenyl | 4-morpholino |
| 50 | 786 | CO ₂ CH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 787 | CO ₂ CH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 788 | CO ₂ CH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |

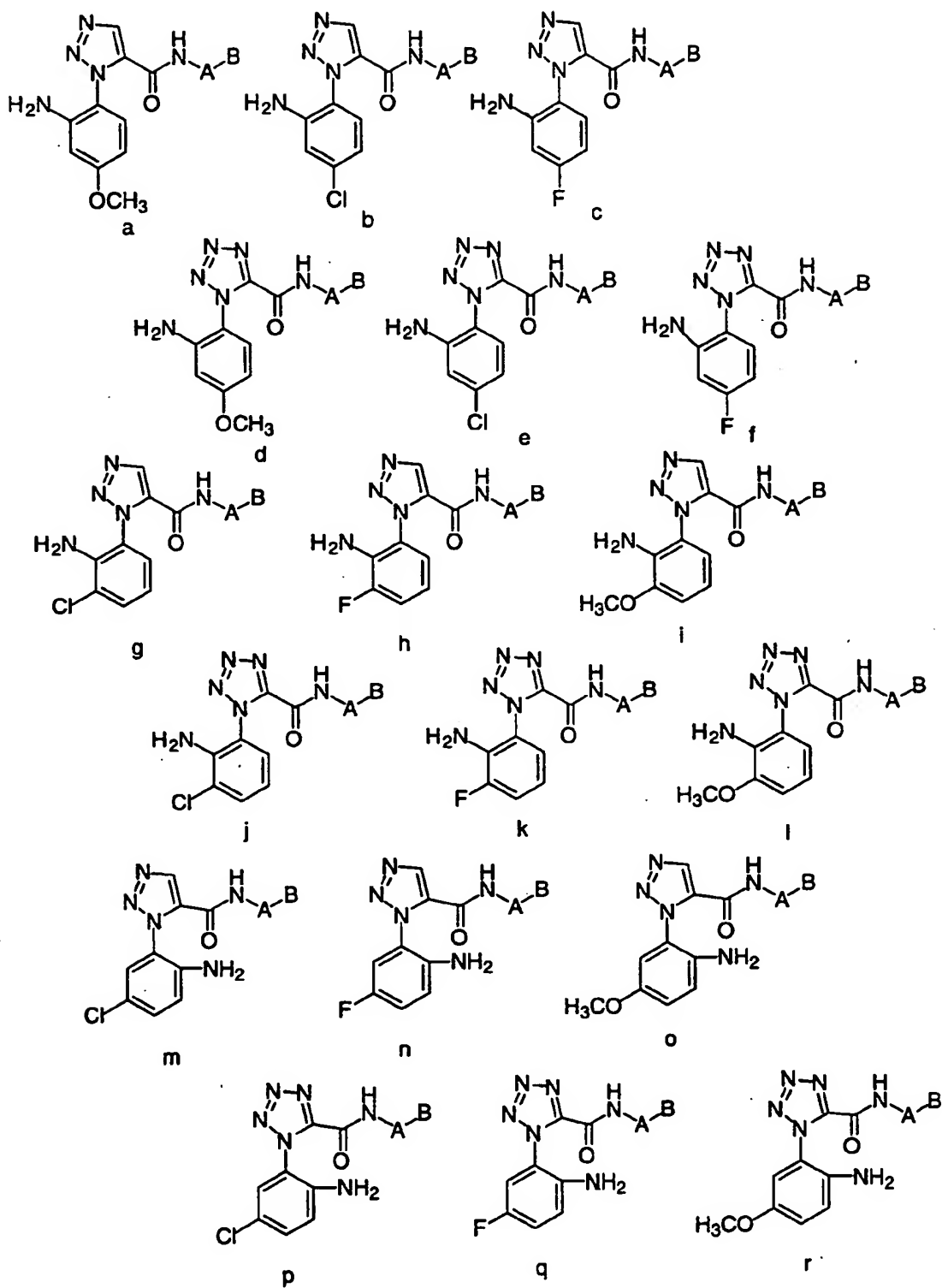
| | | | | |
|----|-----|----------------------------------|----------------|---------------------------------------------|
| | 789 | CO ₂ CH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 790 | CO ₂ CH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 791 | CO ₂ CH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 792 | CO ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| 5 | 793 | CO ₂ CH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 794 | CO ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 795 | CO ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 796 | CO ₂ CH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 797 | CO ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| 10 | 798 | CO ₂ CH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 799 | CO ₂ CH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 800 | CO ₂ CH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 801 | CH ₂ OCH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| | 802 | CH ₂ OCH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| 15 | 803 | CH ₂ OCH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 804 | CH ₂ OCH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 805 | CH ₂ OCH ₃ | phenyl | 4-morpholino |
| | 806 | CH ₂ OCH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 807 | CH ₂ OCH ₃ | phenyl | 4-morpholinocarbonyl |
| 20 | 808 | CH ₂ OCH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 809 | CH ₂ OCH ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 810 | CH ₂ OCH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 811 | CH ₂ OCH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 812 | CH ₂ OCH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| 25 | 813 | CH ₂ OCH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 814 | CH ₂ OCH ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 815 | CH ₂ OCH ₃ | 2-pyridyl | 4-morpholino |
| | 816 | CH ₂ OCH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 817 | CH ₂ OCH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| 30 | 818 | CH ₂ OCH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 819 | CH ₂ OCH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 820 | CH ₂ OCH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 821 | CH ₂ OCH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 822 | CH ₂ OCH ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| 35 | 823 | CH ₂ OCH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 824 | CH ₂ OCH ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 825 | CH ₂ OCH ₃ | 3-pyridyl | 4-morpholino |
| | 826 | CH ₂ OCH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 827 | CH ₂ OCH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| 40 | 828 | CH ₂ OCH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 829 | CH ₂ OCH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 830 | CH ₂ OCH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 831 | CH ₂ OCH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 832 | CH ₂ OCH ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| 45 | 833 | CH ₂ OCH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 834 | CH ₂ OCH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 835 | CH ₂ OCH ₃ | 2-pyrimidyl | 4-morpholino |
| | 836 | CH ₂ OCH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 837 | CH ₂ OCH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| 50 | 838 | CH ₂ OCH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 839 | CH ₂ OCH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 840 | CH ₂ OCH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |

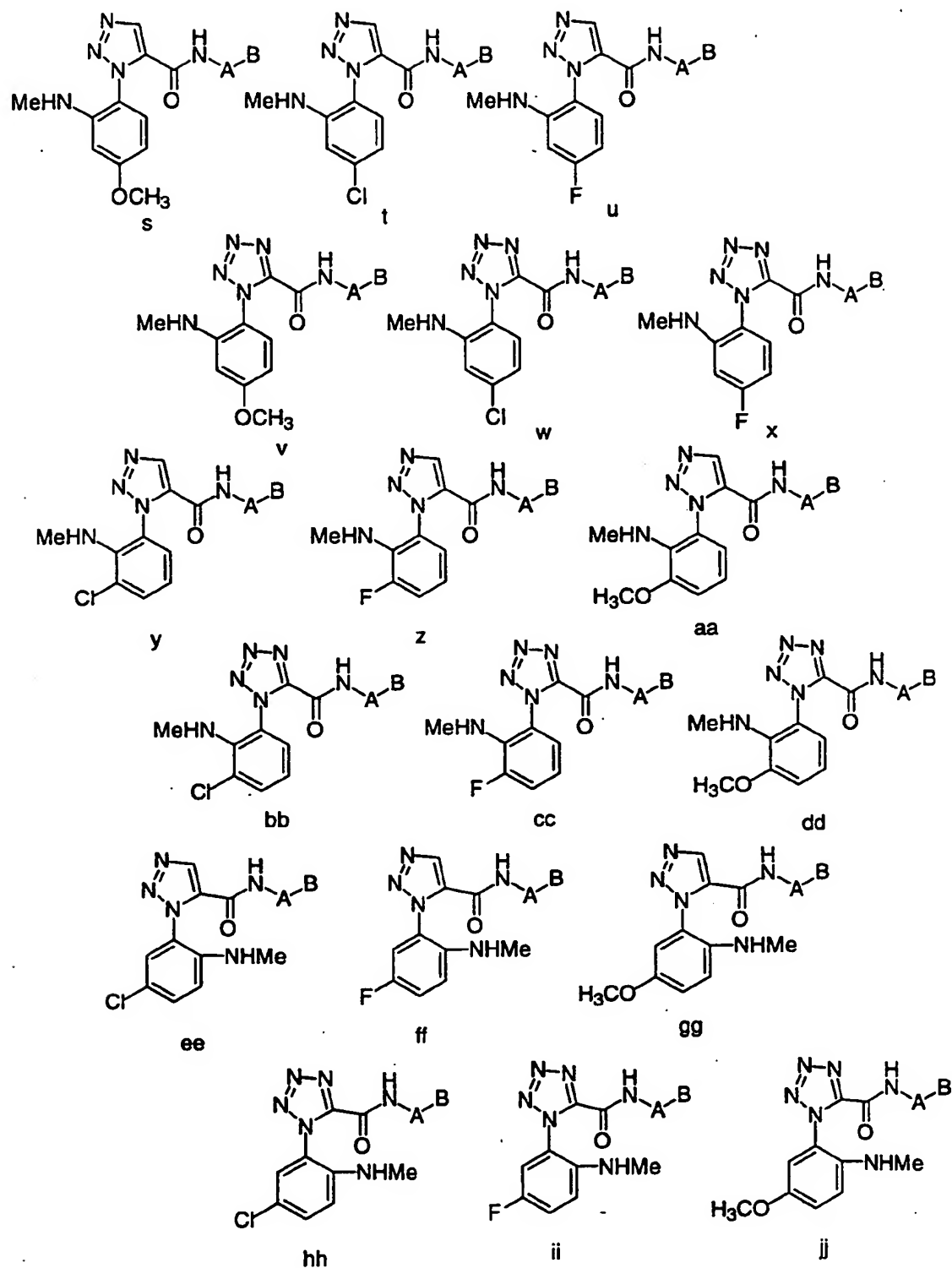
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|----|-----|----------------------------------|----------------|---------------------------------------------|
| | 841 | CH ₂ OCH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 842 | CH ₂ OCH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 843 | CH ₂ OCH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 844 | CH ₂ OCH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 5 | 845 | CH ₂ OCH ₃ | 5-pyrimidyl | 4-morpholino |
| | 846 | CH ₂ OCH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 847 | CH ₂ OCH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 848 | CH ₂ OCH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 849 | CH ₂ OCH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| 10 | 850 | CH ₂ OCH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 851 | CH ₂ OCH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 852 | CH ₂ OCH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 853 | CH ₂ OCH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 854 | CH ₂ OCH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| 15 | 855 | CH ₂ OCH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 856 | CH ₂ OCH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 857 | CH ₂ OCH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 858 | CH ₂ OCH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 859 | CH ₂ OCH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| 20 | 860 | CH ₂ OCH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 861 | CH ₂ OCH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 862 | CH ₂ OCH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 863 | CH ₂ OCH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 864 | CH ₂ OCH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| 25 | 865 | CH ₂ OCH ₃ | 2-F-phenyl | 4-morpholino |
| | 866 | CH ₂ OCH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 867 | CH ₂ OCH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 868 | CH ₂ OCH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 869 | CH ₂ OCH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| 30 | 870 | CH ₂ OCH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 871 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 872 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 873 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 874 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| 35 | 875 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 876 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 877 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 878 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 879 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| 40 | 880 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 881 | CONH ₂ | phenyl | 2-(aminosulfonyl)phenyl |
| | 882 | CONH ₂ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 883 | CONH ₂ | phenyl | 1-pyrrolidinocarbonyl |
| | 884 | CONH ₂ | phenyl | 2-(methylsulfonyl)phenyl |
| 45 | 885 | CONH ₂ | phenyl | 4-morpholino |
| | 886 | CONH ₂ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 887 | CONH ₂ | phenyl | 4-morpholinocarbonyl |
| | 888 | CONH ₂ | phenyl | 2-methyl-1-imidazolyl |
| | 889 | CONH ₂ | phenyl | 5-methyl-1-imidazolyl |
| 50 | 890 | CONH ₂ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 891 | CONH ₂ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 892 | CONH ₂ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |

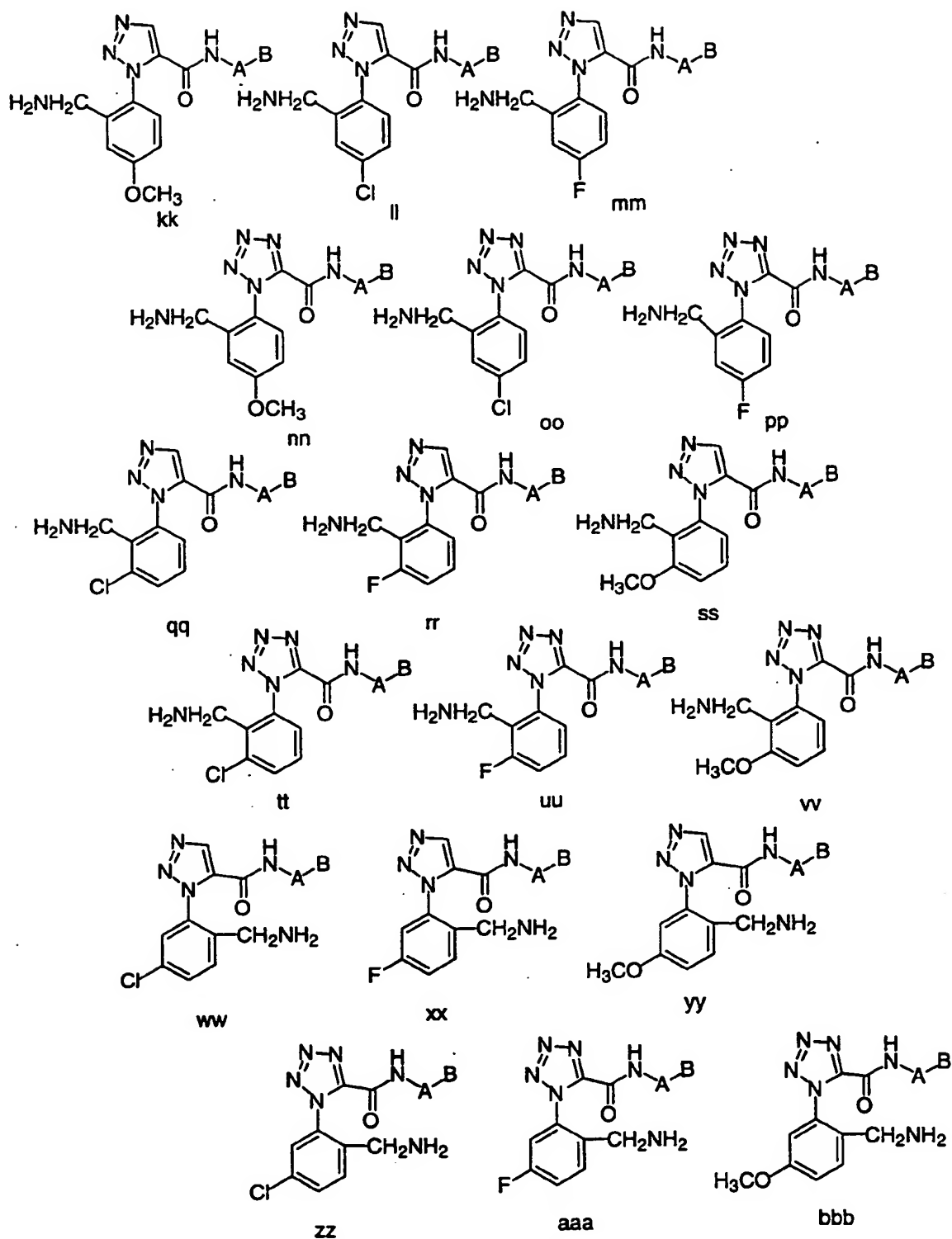
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|----|-----|-------------------|-------------|---------------------------------------------|
| | 893 | CONH ₂ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 894 | CONH ₂ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 895 | CONH ₂ | 2-pyridyl | 4-morpholino |
| | 896 | CONH ₂ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 5 | 897 | CONH ₂ | 2-pyridyl | 4-morpholinocarbonyl |
| | 898 | CONH ₂ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 899 | CONH ₂ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 900 | CONH ₂ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 901 | CONH ₂ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| 10 | 902 | CONH ₂ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 903 | CONH ₂ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 904 | CONH ₂ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 905 | CONH ₂ | 3-pyridyl | 4-morpholino |
| | 906 | CONH ₂ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 15 | 907 | CONH ₂ | 3-pyridyl | 4-morpholinocarbonyl |
| | 908 | CONH ₂ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 909 | CONH ₂ | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 910 | CONH ₂ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 911 | CONH ₂ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 20 | 912 | CONH ₂ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 913 | CONH ₂ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 914 | CONH ₂ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 915 | CONH ₂ | 2-pyrimidyl | 4-morpholino |
| | 916 | CONH ₂ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 25 | 917 | CONH ₂ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 918 | CONH ₂ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 919 | CONH ₂ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 920 | CONH ₂ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 921 | CONH ₂ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 30 | 922 | CONH ₂ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 923 | CONH ₂ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 924 | CONH ₂ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 925 | CONH ₂ | 5-pyrimidyl | 4-morpholino |
| | 926 | CONH ₂ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 35 | 927 | CONH ₂ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 928 | CONH ₂ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 929 | CONH ₂ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 930 | CONH ₂ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 931 | CONH ₂ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| 40 | 932 | CONH ₂ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 933 | CONH ₂ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 934 | CONH ₂ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 935 | CONH ₂ | 2-Cl-phenyl | 4-morpholino |
| | 936 | CONH ₂ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 45 | 937 | CONH ₂ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 938 | CONH ₂ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 939 | CONH ₂ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 940 | CONH ₂ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 941 | CONH ₂ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| 50 | 942 | CONH ₂ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 943 | CONH ₂ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 944 | CONH ₂ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |

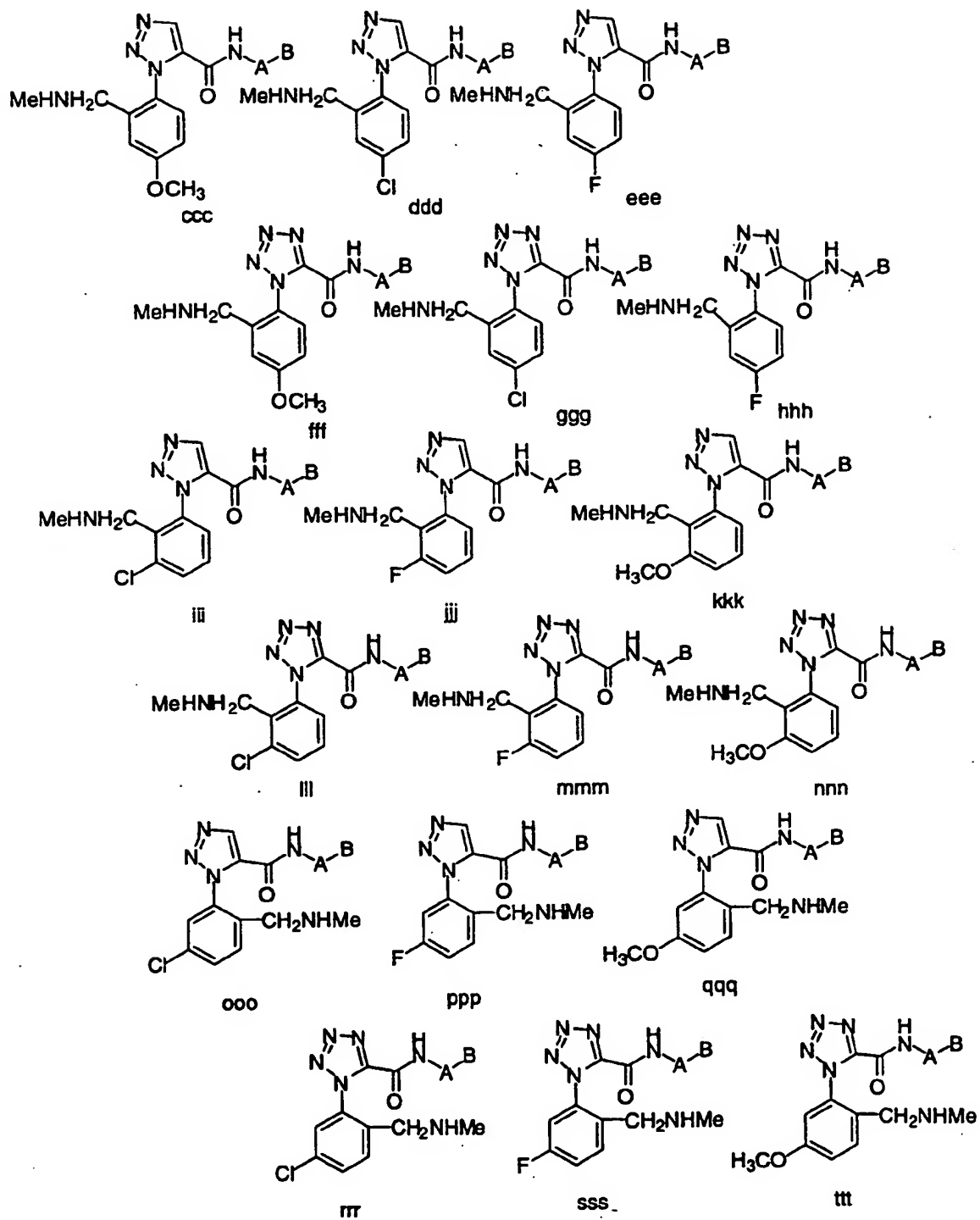
| | | | | |
|----|-----|-------------------|----------------|---------------------------------------------|
| | 945 | CONH ₂ | 2-F-phenyl | 4-morpholino |
| | 946 | CONH ₂ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 947 | CONH ₂ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 948 | CONH ₂ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| 5 | 949 | CONH ₂ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 950 | CONH ₂ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 951 | CONH ₂ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 952 | CONH ₂ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 953 | CONH ₂ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| 10 | 954 | CONH ₂ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 955 | CONH ₂ | 2,6-diF-phenyl | 4-morpholino |
| | 956 | CONH ₂ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 957 | CONH ₂ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 958 | CONH ₂ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| 15 | 959 | CONH ₂ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 960 | CONH ₂ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |

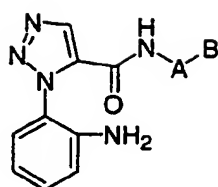
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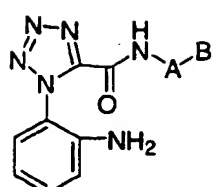




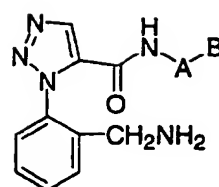




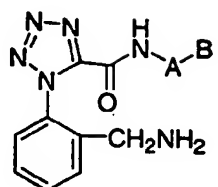
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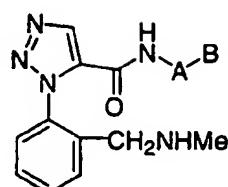
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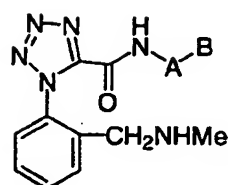
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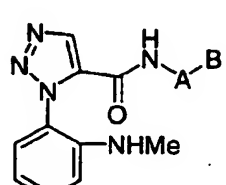
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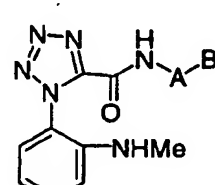
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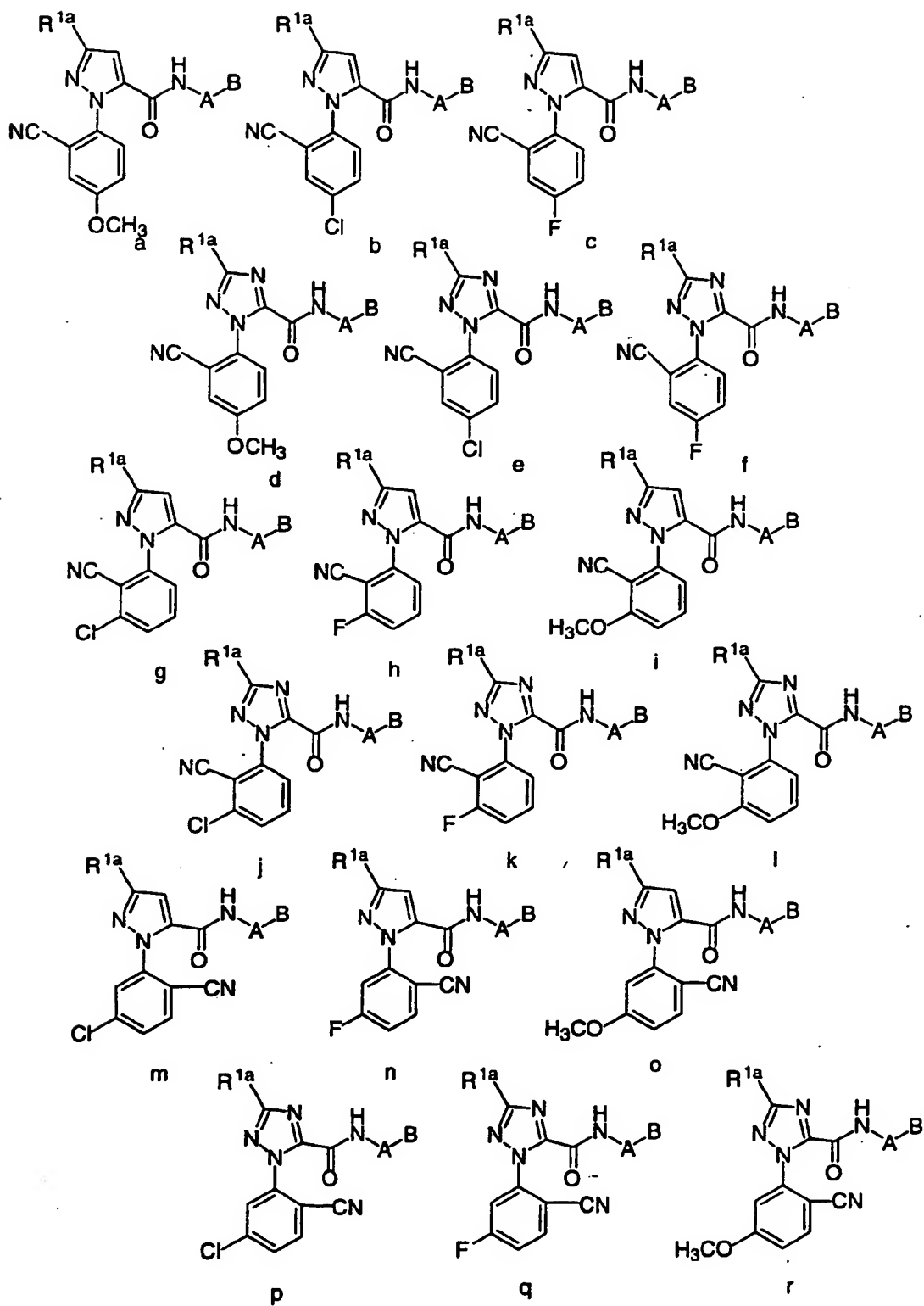


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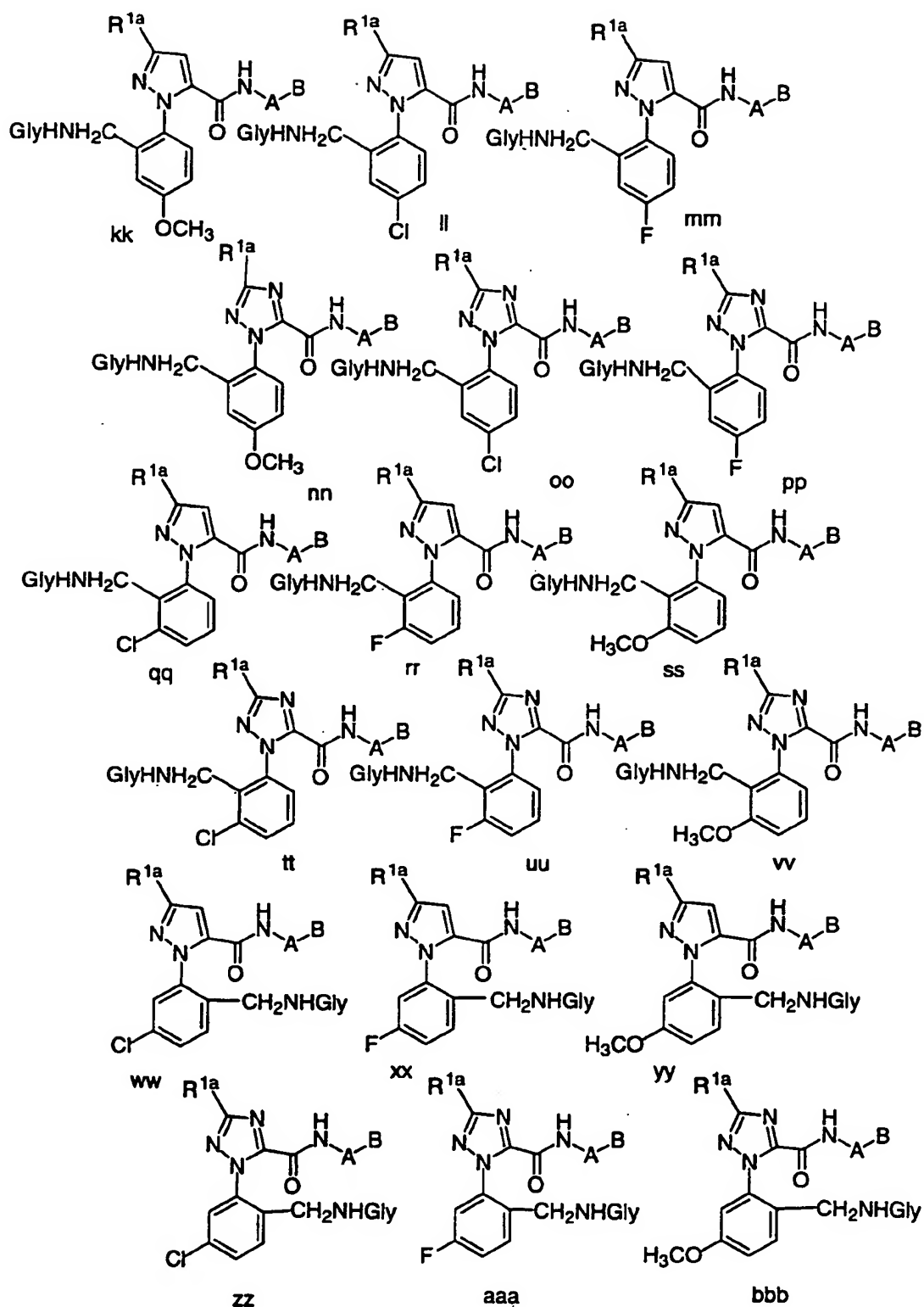
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| 5 | 1 phenyl | 2-(aminosulfonyl)phenyl |
| | 2 phenyl | 2-(methylaminosulfonyl)phenyl |
| | 3 phenyl | 1-pyrrolidinocarbonyl |
| | 4 phenyl | 2-(methylsulfonyl)phenyl |
| | 5 phenyl | 4-morpholino |
| 10 | 6 phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 7 phenyl | 4-morpholinocarbonyl |
| | 8 phenyl | 2-methyl-1-imidazolyl |
| | 9 phenyl | 5-methyl-1-imidazolyl |
| | 10 phenyl | 2-methylsulfonyl-1-imidazolyl |
| 15 | 11 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 12 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 13 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 14 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 15 2-pyridyl | 4-morpholino |
| 20 | 16 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 17 2-pyridyl | 4-morpholinocarbonyl |
| | 18 2-pyridyl | 2-methyl-1-imidazolyl |
| | 19 2-pyridyl | 5-methyl-1-imidazolyl |
| | 20 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| 25 | 21 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 22 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 23 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 24 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 25 3-pyridyl | 4-morpholino |
| 30 | 26 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 27 3-pyridyl | 4-morpholinocarbonyl |

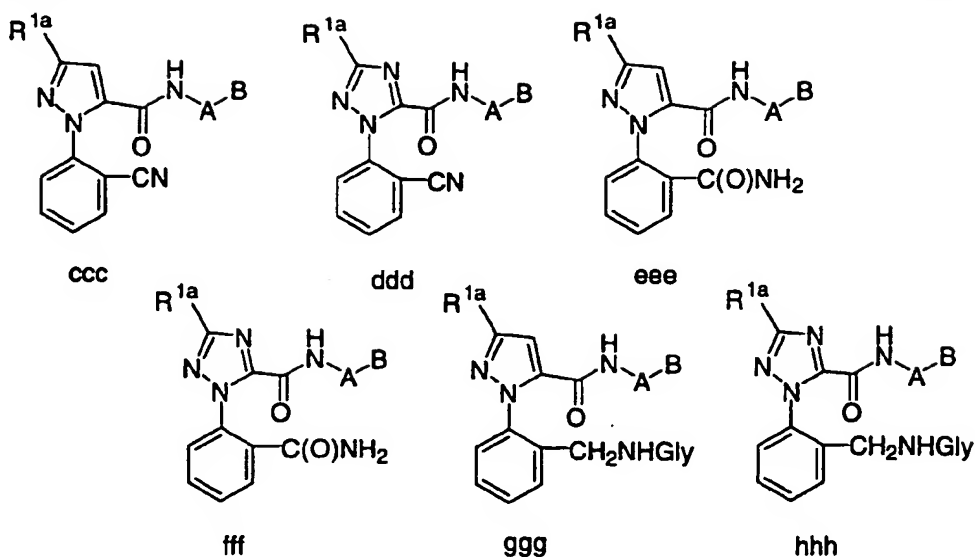
| | | | |
|----|----|----------------|---------------------------------------------|
| | 28 | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 29 | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 30 | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 31 | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 5 | 32 | 2-pyrimidyl | 2-(methyaminosulfonyl)phenyl |
| | 33 | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 34 | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 35 | 2-pyrimidyl | 4-morpholino |
| | 36 | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 10 | 37 | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 38 | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 39 | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 40 | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 41 | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 15 | 42 | 5-pyrimidyl | 2-(methyaminosulfonyl)phenyl |
| | 43 | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 44 | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 45 | 5-pyrimidyl | 4-morpholino |
| | 46 | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 20 | 47 | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 48 | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 49 | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 50 | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 51 | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| 25 | 52 | 2-Cl-phenyl | 2-(methyaminosulfonyl)phenyl |
| | 53 | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 54 | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 55 | 2-Cl-phenyl | 4-morpholino |
| | 56 | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 30 | 57 | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 58 | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 59 | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 60 | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 61 | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| 35 | 62 | 2-F-phenyl | 2-(methyaminosulfonyl)phenyl |
| | 63 | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 64 | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 65 | 2-F-phenyl | 4-morpholino |
| | 66 | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 40 | 67 | 2-F-phenyl | 4-morpholinocarbonyl |
| | 68 | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 69 | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 70 | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 71 | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| 45 | 72 | 2,6-diF-phenyl | 2-(methyaminosulfonyl)phenyl |
| | 73 | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 74 | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 75 | 2,6-diF-phenyl | 4-morpholino |
| | 76 | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 50 | 77 | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 78 | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 79 | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 80 | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |

Table 4









| Ex # | R ^{1a} | A | B |
|------|--------------------|-------------|---------------------------------------------|
| 5 | 1 CH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| | 2 CH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 3 CH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 4 CH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 5 CH ₃ | phenyl | 4-morpholino |
| | 6 CH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 10 | 7 CH ₃ | phenyl | 4-morpholinocarbonyl |
| | 8 CH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 9 CH ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 10 CH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 11 CH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| 15 | 12 CH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 13 CH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 14 CH ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 15 CH ₃ | 2-pyridyl | 4-morpholino |
| | 16 CH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 20 | 17 CH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| | 18 CH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 19 CH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 20 CH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 21 CH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| 25 | 22 CH ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 23 CH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 24 CH ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 25 CH ₃ | 3-pyridyl | 4-morpholino |
| | 26 CH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 30 | 27 CH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| | 28 CH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 29 CH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 30 CH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 31 CH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 35 | 32 CH ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 33 CH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |

| | | | | |
|----|----|---------------------------------|----------------|---------------------------------------------|
| | 34 | CH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 35 | CH ₃ | 2-pyrimidyl | 4-morpholino |
| | 36 | CH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 37 | CH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| 5 | 38 | CH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 39 | CH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 40 | CH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 41 | CH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 42 | CH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| 10 | 43 | CH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 44 | CH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 45 | CH ₃ | 5-pyrimidyl | 4-morpholino |
| | 46 | CH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 47 | CH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| 15 | 48 | CH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 49 | CH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 50 | CH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 51 | CH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 52 | CH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| 20 | 53 | CH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 54 | CH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 55 | CH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 56 | CH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 57 | CH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| 25 | 58 | CH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 59 | CH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 60 | CH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 61 | CH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 62 | CH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| 30 | 63 | CH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 64 | CH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 65 | CH ₃ | 2-F-phenyl | 4-morpholino |
| | 66 | CH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 67 | CH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| 35 | 68 | CH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 69 | CH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 70 | CH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 71 | CH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 72 | CH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| 40 | 73 | CH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 74 | CH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 75 | CH ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 76 | CH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 77 | CH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| 45 | 78 | CH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 79 | CH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 80 | CH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 81 | CH ₂ CH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| | 82 | CH ₂ CH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| 50 | 83 | CH ₂ CH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 84 | CH ₂ CH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 85 | CH ₂ CH ₃ | phenyl | 4-morpholino |

| | | | |
|--------|---------------------------------|-------------|---------------------------------------------|
| 86 | CH ₂ CH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 87 | CH ₂ CH ₃ | phenyl | 4-morpholinocarbonyl |
| 88 | CH ₂ CH ₃ | phenyl | 2-methyl-1-imidazolyl |
| 89 | CH ₂ CH ₃ | phenyl | 5-methyl-1-imidazolyl |
| 5 90 | CH ₂ CH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| 91 | CH ₂ CH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| 92 | CH ₂ CH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| 93 | CH ₂ CH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| 94 | CH ₂ CH ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| 10 95 | CH ₂ CH ₃ | 2-pyridyl | 4-morpholino |
| 96 | CH ₂ CH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 97 | CH ₂ CH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| 98 | CH ₂ CH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| 99 | CH ₂ CH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| 15 100 | CH ₂ CH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| 101 | CH ₂ CH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| 102 | CH ₂ CH ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| 103 | CH ₂ CH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| 104 | CH ₂ CH ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| 20 105 | CH ₂ CH ₃ | 3-pyridyl | 4-morpholino |
| 106 | CH ₂ CH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 107 | CH ₂ CH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| 108 | CH ₂ CH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| 109 | CH ₂ CH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| 25 110 | CH ₂ CH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| 111 | CH ₂ CH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 112 | CH ₂ CH ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| 113 | CH ₂ CH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| 114 | CH ₂ CH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 30 115 | CH ₂ CH ₃ | 2-pyrimidyl | 4-morpholino |
| 116 | CH ₂ CH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 117 | CH ₂ CH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| 118 | CH ₂ CH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| 119 | CH ₂ CH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| 35 120 | CH ₂ CH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| 121 | CH ₂ CH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 122 | CH ₂ CH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| 123 | CH ₂ CH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| 124 | CH ₂ CH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 40 125 | CH ₂ CH ₃ | 5-pyrimidyl | 4-morpholino |
| 126 | CH ₂ CH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 127 | CH ₂ CH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| 128 | CH ₂ CH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| 129 | CH ₂ CH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| 45 130 | CH ₂ CH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| 131 | CH ₂ CH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| 132 | CH ₂ CH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| 133 | CH ₂ CH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| 134 | CH ₂ CH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| 50 135 | CH ₂ CH ₃ | 2-Cl-phenyl | 4-morpholino |
| 136 | CH ₂ CH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 137 | CH ₂ CH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |

| | | | | |
|----|-----|---------------------------------|----------------|---------------------------------------------|
| | 138 | CH ₂ CH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 139 | CH ₂ CH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 140 | CH ₂ CH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 141 | CH ₂ CH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| 5 | 142 | CH ₂ CH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 143 | CH ₂ CH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 144 | CH ₂ CH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 145 | CH ₂ CH ₃ | 2-F-phenyl | 4-morpholino |
| | 146 | CH ₂ CH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 10 | 147 | CH ₂ CH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 148 | CH ₂ CH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 149 | CH ₂ CH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 150 | CH ₂ CH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 151 | CH ₂ CH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| 15 | 152 | CH ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 153 | CH ₂ CH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 154 | CH ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 155 | CH ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 156 | CH ₂ CH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 20 | 157 | CH ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 158 | CH ₂ CH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 159 | CH ₂ CH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 160 | CH ₂ CH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 161 | CF ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| 25 | 162 | CF ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 163 | CF ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 164 | CF ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 165 | CF ₃ | phenyl | 4-morpholino |
| | 166 | CF ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 30 | 167 | CF ₃ | phenyl | 4-morpholinocarbonyl |
| | 168 | CF ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 169 | CF ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 170 | CF ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 171 | CF ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| 35 | 172 | CF ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 173 | CF ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 174 | CF ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 175 | CF ₃ | 2-pyridyl | 4-morpholino |
| | 176 | CF ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 40 | 177 | CF ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| | 178 | CF ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 179 | CF ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 180 | CF ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 181 | CF ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| 45 | 182 | CF ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 183 | CF ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 184 | CF ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 185 | CF ₃ | 3-pyridyl | 4-morpholino |
| | 186 | CF ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 50 | 187 | CF ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| | 188 | CF ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 189 | CF ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |

| | | | | |
|----|-----|------------------|----------------|---------------------------------------------|
| | 190 | CF ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 191 | CF ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 192 | CF ₃ | 2-pyrimidyl | 2-(methyaminosulfonyl)phenyl |
| | 193 | CF ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| 5 | 194 | CF ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 195 | CF ₃ | 2-pyrimidyl | 4-morpholino |
| | 196 | CF ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 197 | CF ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 198 | CF ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| 10 | 199 | CF ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 200 | CF ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 201 | CF ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 202 | CF ₃ | 5-pyrimidyl | 2-(methyaminosulfonyl)phenyl |
| | 203 | CF ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| 15 | 204 | CF ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 205 | CF ₃ | 5-pyrimidyl | 4-morpholino |
| | 206 | CF ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 207 | CF ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 208 | CF ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| 20 | 209 | CF ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 210 | CF ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 211 | CF ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 212 | CF ₃ | 2-Cl-phenyl | 2-(methyaminosulfonyl)phenyl |
| | 213 | CF ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| 25 | 214 | CF ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 215 | CF ₃ | 2-Cl-phenyl | 4-morpholino |
| | 216 | CF ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 217 | CF ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 218 | CF ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| 30 | 219 | CF ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 220 | CF ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 221 | CF ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 222 | CF ₃ | 2-F-phenyl | 2-(methyaminosulfonyl)phenyl |
| | 223 | CF ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| 35 | 224 | CF ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 225 | CF ₃ | 2-F-phenyl | 4-morpholino |
| | 226 | CF ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 227 | CF ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 228 | CF ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| 40 | 229 | CF ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 230 | CF ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 231 | CF ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 232 | CF ₃ | 2,6-diF-phenyl | 2-(methyaminosulfonyl)phenyl |
| | 233 | CF ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| 45 | 234 | CF ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 235 | CF ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 236 | CF ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 237 | CF ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 238 | CF ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| 50 | 239 | CF ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 240 | CF ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 241 | SCH ₃ | phenyl | 2-(aminosulfonyl)phenyl |

| | | | | |
|----|-----|------------------|-------------|---------------------------------------------|
| | 242 | SCH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 243 | SCH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 244 | SCH ₃ | phenyl | 2-(methysulfonyl)phenyl |
| | 245 | SCH ₃ | phenyl | 4-morpholino |
| 5 | 246 | SCH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 247 | SCH ₃ | phenyl | 4-morpholinocarbonyl |
| | 248 | SCH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 249 | SCH ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 250 | SCH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| 10 | 251 | SCH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 252 | SCH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 253 | SCH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 254 | SCH ₃ | 2-pyridyl | 2-(methysulfonyl)phenyl |
| | 255 | SCH ₃ | 2-pyridyl | 4-morpholino |
| 15 | 256 | SCH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 257 | SCH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| | 258 | SCH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 259 | SCH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 260 | SCH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| 20 | 261 | SCH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 262 | SCH ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 263 | SCH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 264 | SCH ₃ | 3-pyridyl | 2-(methysulfonyl)phenyl |
| | 265 | SCH ₃ | 3-pyridyl | 4-morpholino |
| 25 | 266 | SCH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 267 | SCH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| | 268 | SCH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 269 | SCH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 270 | SCH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| 30 | 271 | SCH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 272 | SCH ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 273 | SCH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 274 | SCH ₃ | 2-pyrimidyl | 2-(methysulfonyl)phenyl |
| | 275 | SCH ₃ | 2-pyrimidyl | 4-morpholino |
| 35 | 276 | SCH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 277 | SCH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 278 | SCH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 279 | SCH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 280 | SCH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| 40 | 281 | SCH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 282 | SCH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 283 | SCH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 284 | SCH ₃ | 5-pyrimidyl | 2-(methysulfonyl)phenyl |
| | 285 | SCH ₃ | 5-pyrimidyl | 4-morpholino |
| 45 | 286 | SCH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 287 | SCH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 288 | SCH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 289 | SCH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 290 | SCH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| 50 | 291 | SCH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 292 | SCH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 293 | SCH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |

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|----|-----|-------------------|----------------|---------------------------------------------|
| | 294 | SCH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 295 | SCH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 296 | SCH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 297 | SCH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| 5 | 298 | SCH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 299 | SCH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 300 | SCH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 301 | SCH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 302 | SCH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| 10 | 303 | SCH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 304 | SCH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 305 | SCH ₃ | 2-F-phenyl | 4-morpholino |
| | 306 | SCH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 307 | SCH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| 15 | 308 | SCH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 309 | SCH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 310 | SCH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 311 | SCH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 312 | SCH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| 20 | 313 | SCH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 314 | SCH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 315 | SCH ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 316 | SCH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 317 | SCH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| 25 | 318 | SCH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 319 | SCH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 320 | SCH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 321 | SOCH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| | 322 | SOCH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| 30 | 323 | SOCH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 324 | SOCH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 325 | SOCH ₃ | phenyl | 4-morpholino |
| | 326 | SOCH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 327 | SOCH ₃ | phenyl | 4-morpholinocarbonyl |
| 35 | 328 | SOCH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 329 | SOCH ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 330 | SOCH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 331 | SOCH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 332 | SOCH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| 40 | 333 | SOCH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 334 | SOCH ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 335 | SOCH ₃ | 2-pyridyl | 4-morpholino |
| | 336 | SOCH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 337 | SOCH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| 45 | 338 | SOCH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 339 | SOCH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 340 | SOCH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 341 | SOCH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 342 | SOCH ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| 50 | 343 | SOCH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 344 | SOCH ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 345 | SOCH ₃ | 3-pyridyl | 4-morpholino |

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|----|-----|-------------------|----------------|---------------------------------------------|
| | 346 | SOCH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 347 | SOCH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| | 348 | SOCH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 349 | SOCH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| 5 | 350 | SOCH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 351 | SOCH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 352 | SOCH ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 353 | SOCH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 354 | SOCH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 10 | 355 | SOCH ₃ | 2-pyrimidyl | 4-morpholino |
| | 356 | SOCH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 357 | SOCH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 358 | SOCH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 359 | SOCH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| 15 | 360 | SOCH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 361 | SOCH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 362 | SOCH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 363 | SOCH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 364 | SOCH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 20 | 365 | SOCH ₃ | 5-pyrimidyl | 4-morpholino |
| | 366 | SOCH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 367 | SOCH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 368 | SOCH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 369 | SOCH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| 25 | 370 | SOCH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 371 | SOCH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 372 | SOCH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 373 | SOCH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 374 | SOCH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| 30 | 375 | SOCH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 376 | SOCH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 377 | SOCH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 378 | SOCH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 379 | SOCH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| 35 | 380 | SOCH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 381 | SOCH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 382 | SOCH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 383 | SOCH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 384 | SOCH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| 40 | 385 | SOCH ₃ | 2-F-phenyl | 4-morpholino |
| | 386 | SOCH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 387 | SOCH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 388 | SOCH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 389 | SOCH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| 45 | 390 | SOCH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 391 | SOCH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 392 | SOCH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 393 | SOCH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 394 | SOCH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| 50 | 395 | SOCH ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 396 | SOCH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 397 | SOCH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |

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|----|-----|---------------------------------|----------------|---------------------------------------------|
| | 398 | SOCH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 399 | SOCH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 400 | SOCH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 401 | SO ₂ CH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| 5 | 402 | SO ₂ CH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 403 | SO ₂ CH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 404 | SO ₂ CH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 405 | SO ₂ CH ₃ | phenyl | 4-morpholino |
| | 406 | SO ₂ CH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 10 | 407 | SO ₂ CH ₃ | phenyl | 4-morpholinocarbonyl |
| | 408 | SO ₂ CH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 409 | SO ₂ CH ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 410 | SO ₂ CH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 411 | SO ₂ CH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| 15 | 412 | SO ₂ CH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 413 | SO ₂ CH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 414 | SO ₂ CH ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 415 | SO ₂ CH ₃ | 2-pyridyl | 4-morpholino |
| | 416 | SO ₂ CH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 20 | 417 | SO ₂ CH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| | 418 | SO ₂ CH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 419 | SO ₂ CH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 420 | SO ₂ CH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 421 | SO ₂ CH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| 25 | 422 | SO ₂ CH ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 423 | SO ₂ CH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 424 | SO ₂ CH ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 425 | SO ₂ CH ₃ | 3-pyridyl | 4-morpholino |
| | 426 | SO ₂ CH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 30 | 427 | SO ₂ CH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| | 428 | SO ₂ CH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 429 | SO ₂ CH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 430 | SO ₂ CH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 431 | SO ₂ CH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 35 | 432 | SO ₂ CH ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 433 | SO ₂ CH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 434 | SO ₂ CH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 435 | SO ₂ CH ₃ | 2-pyrimidyl | 4-morpholino |
| | 436 | SO ₂ CH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 40 | 437 | SO ₂ CH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 438 | SO ₂ CH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 439 | SO ₂ CH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 440 | SO ₂ CH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 441 | SO ₂ CH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 45 | 442 | SO ₂ CH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 443 | SO ₂ CH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 444 | SO ₂ CH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 445 | SO ₂ CH ₃ | 5-pyrimidyl | 4-morpholino |
| | 446 | SO ₂ CH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 50 | 447 | SO ₂ CH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 448 | SO ₂ CH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 449 | SO ₂ CH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |

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|----|-----|--------------------------------------------------------|----------------|---------------------------------------------|
| | 450 | SO ₂ CH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 451 | SO ₂ CH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 452 | SO ₂ CH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 453 | SO ₂ CH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| 5 | 454 | SO ₂ CH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 455 | SO ₂ CH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 456 | SO ₂ CH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 457 | SO ₂ CH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 458 | SO ₂ CH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| 10 | 459 | SO ₂ CH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 460 | SO ₂ CH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 461 | SO ₂ CH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 462 | SO ₂ CH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 463 | SO ₂ CH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| 15 | 464 | SO ₂ CH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 465 | SO ₂ CH ₃ | 2-F-phenyl | 4-morpholino |
| | 466 | SO ₂ CH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 467 | SO ₂ CH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 468 | SO ₂ CH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| 20 | 469 | SO ₂ CH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 470 | SO ₂ CH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 471 | SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 472 | SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 473 | SO ₂ CH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| 25 | 474 | SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 475 | SO ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 476 | SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 477 | SO ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 478 | SO ₂ CH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| 30 | 479 | SO ₂ CH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 480 | SO ₂ CH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 481 | CH ₂ NH -SO ₂ CH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| | 482 | CH ₂ NH -SO ₂ CH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| 35 | 483 | CH ₂ NH -SO ₂ CH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 484 | CH ₂ NH -SO ₂ CH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| 40 | 485 | CH ₂ NH -SO ₂ CH ₃ | phenyl | 4-morpholino |
| | 486 | CH ₂ NH -SO ₂ CH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 487 | CH ₂ NH -SO ₂ CH ₃ | phenyl | 4-morpholinocarbonyl |
| 45 | 488 | CH ₂ NH -SO ₂ CH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 489 | CH ₂ NH -SO ₂ CH ₃ | phenyl | 5-methyl-1-imidazolyl |
| 50 | 490 | CH ₂ NH -SO ₂ CH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 491 | CH ₂ NH | 2-pyridyl | 2-(aminosulfonyl)phenyl |

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|----|-----|----------------------------------|-------------|---------------------------------------------|
| | | -SO ₂ CH ₃ | | |
| | 492 | CH ₂ NH | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 493 | CH ₂ NH | 2-pyridyl | 1-pyrrolidinocarbonyl |
| 5 | | -SO ₂ CH ₃ | | |
| | 494 | CH ₂ NH | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 495 | CH ₂ NH | 2-pyridyl | 4-morpholino |
| | | -SO ₂ CH ₃ | | |
| 10 | 496 | CH ₂ NH | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 497 | CH ₂ NH | 2-pyridyl | 4-morpholinocarbonyl |
| | | -SO ₂ CH ₃ | | |
| | 498 | CH ₂ NH | 2-pyridyl | 2-methyl-1-imidazolyl |
| 15 | | -SO ₂ CH ₃ | | |
| | 499 | CH ₂ NH | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 500 | CH ₂ NH | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | | -SO ₂ CH ₃ | | |
| | 501 | CH ₂ NH | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| 20 | | -SO ₂ CH ₃ | | |
| | 502 | CH ₂ NH | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 503 | CH ₂ NH | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | | -SO ₂ CH ₃ | | |
| 25 | 504 | CH ₂ NH | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 505 | CH ₂ NH | 3-pyridyl | 4-morpholino |
| | | -SO ₂ CH ₃ | | |
| | 506 | CH ₂ NH | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 30 | | -SO ₂ CH ₃ | | |
| | 507 | CH ₂ NH | 3-pyridyl | 4-morpholinocarbonyl |
| | | -SO ₂ CH ₃ | | |
| | 508 | CH ₂ NH | 3-pyridyl | 2-methyl-1-imidazolyl |
| | | -SO ₂ CH ₃ | | |
| 35 | 509 | CH ₂ NH | 3-pyridyl | 5-methyl-1-imidazolyl |
| | | -SO ₂ CH ₃ | | |
| | 510 | CH ₂ NH | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | | -SO ₂ CH ₃ | | |
| | 511 | CH ₂ NH | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 40 | | -SO ₂ CH ₃ | | |
| | 512 | CH ₂ NH | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 513 | CH ₂ NH | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | | -SO ₂ CH ₃ | | |
| 45 | 514 | CH ₂ NH | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | | -SO ₂ CH ₃ | | |
| | 515 | CH ₂ NH | 2-pyrimidyl | 4-morpholino |
| | | -SO ₂ CH ₃ | | |
| | 516 | CH ₂ NH | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 50 | | -SO ₂ CH ₃ | | |
| | 517 | CH ₂ NH | 2-pyrimidyl | 4-morpholinocarbonyl |
| | | -SO ₂ CH ₃ | | |

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|----|-----|--------------------------------------------------------|-------------|---------------------------------------------|
| | 518 | CH ₂ NH -SO ₂ CH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 519 | CH ₂ NH -SO ₂ CH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| 5 | 520 | CH ₂ NH -SO ₂ CH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 521 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 10 | 522 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 523 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 524 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 15 | 525 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 4-morpholino |
| | 526 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 20 | 527 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 528 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 529 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| 25 | 530 | CH ₂ NH -SO ₂ CH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 531 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| 30 | 532 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 533 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 534 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| 35 | 535 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 536 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 40 | 537 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 538 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 539 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| 45 | 540 | CH ₂ NH -SO ₂ CH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 541 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| 50 | 542 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 543 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |

| | | | | |
|----|-----|--------------------------------------------------------|----------------|---------------------------------------------|
| | 544 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 545 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 4-morpholino |
| 5 | 546 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 547 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 548 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| 10 | 549 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 550 | CH ₂ NH -SO ₂ CH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 15 | 551 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 552 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 553 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| 20 | 554 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 555 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholino |
| 25 | 556 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 557 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 558 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| 30 | 559 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 560 | CH ₂ NH -SO ₂ CH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 35 | 561 | Cl | phenyl | 2-(aminosulfonyl)phenyl |
| | 562 | Cl | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 563 | Cl | phenyl | 1-pyrrolidinocarbonyl |
| | 564 | Cl | phenyl | 2-(methylsulfonyl)phenyl |
| | 565 | Cl | phenyl | 4-morpholino |
| 40 | 566 | Cl | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 567 | Cl | phenyl | 4-morpholinocarbonyl |
| | 568 | Cl | phenyl | 2-methyl-1-imidazolyl |
| | 569 | Cl | phenyl | 5-methyl-1-imidazolyl |
| | 570 | Cl | phenyl | 2-methylsulfonyl-1-imidazolyl |
| 45 | 571 | Cl | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 572 | Cl | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 573 | Cl | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 574 | Cl | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 575 | Cl | 2-pyridyl | 4-morpholino |
| 50 | 576 | Cl | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 577 | Cl | 2-pyridyl | 4-morpholinocarbonyl |
| | 578 | Cl | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 579 | Cl | 2-pyridyl | 5-methyl-1-imidazolyl |

| | | | | |
|----|-----|----|----------------|---------------------------------------------|
| | 580 | Cl | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 581 | Cl | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 582 | Cl | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 583 | Cl | 3-pyridyl | 1-pyrrolidinocarbonyl |
| 5 | 584 | Cl | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 585 | Cl | 3-pyridyl | 4-morpholino |
| | 586 | Cl | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 587 | Cl | 3-pyridyl | 4-morpholinocarbonyl |
| | 588 | Cl | 3-pyridyl | 2-methyl-1-imidazolyl |
| 10 | 589 | Cl | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 590 | Cl | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 591 | Cl | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 592 | Cl | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 593 | Cl | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| 15 | 594 | Cl | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 595 | Cl | 2-pyrimidyl | 4-morpholino |
| | 596 | Cl | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 597 | Cl | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 598 | Cl | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| 20 | 599 | Cl | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 600 | Cl | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 601 | Cl | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 602 | Cl | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 603 | Cl | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| 25 | 604 | Cl | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 605 | Cl | 5-pyrimidyl | 4-morpholino |
| | 606 | Cl | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 607 | Cl | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 608 | Cl | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| 30 | 609 | Cl | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 610 | Cl | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 611 | Cl | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 612 | Cl | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 613 | Cl | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| 35 | 614 | Cl | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 615 | Cl | 2-Cl-phenyl | 4-morpholino |
| | 616 | Cl | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 617 | Cl | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 618 | Cl | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| 40 | 619 | Cl | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 620 | Cl | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 621 | Cl | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 622 | Cl | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 623 | Cl | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| 45 | 624 | Cl | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 625 | Cl | 2-F-phenyl | 4-morpholino |
| | 626 | Cl | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 627 | Cl | 2-F-phenyl | 4-morpholinocarbonyl |
| | 628 | Cl | 2-F-phenyl | 2-methyl-1-imidazolyl |
| 50 | 629 | Cl | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 630 | Cl | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 631 | Cl | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 632 | Cl | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 633 | Cl | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| 55 | 634 | Cl | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 635 | Cl | 2,6-diF-phenyl | 4-morpholino |

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|----|-----|----|----------------|---------------------------------------------|
| | 636 | Cl | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 637 | Cl | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 638 | Cl | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 639 | Cl | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| 5 | 640 | Cl | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 641 | F | phenyl | 2-(aminosulfonyl)phenyl |
| | 642 | F | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 643 | F | phenyl | 1-pyrrolidinocarbonyl |
| | 644 | F | phenyl | 2-(methylsulfonyl)phenyl |
| 10 | 645 | F | phenyl | 4-morpholino |
| | 646 | F | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 647 | F | phenyl | 4-morpholinocarbonyl |
| | 648 | F | phenyl | 2-methyl-1-imidazolyl |
| | 649 | F | phenyl | 5-methyl-1-imidazolyl |
| 15 | 650 | F | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 651 | F | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 652 | F | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 653 | F | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 654 | F | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| 20 | 655 | F | 2-pyridyl | 4-morpholino |
| | 656 | F | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 657 | F | 2-pyridyl | 4-morpholinocarbonyl |
| | 658 | F | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 659 | F | 2-pyridyl | 5-methyl-1-imidazolyl |
| 25 | 660 | F | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 661 | F | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 662 | F | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 663 | F | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 664 | F | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| 30 | 665 | F | 3-pyridyl | 4-morpholino |
| | 666 | F | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 667 | F | 3-pyridyl | 4-morpholinocarbonyl |
| | 668 | F | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 669 | F | 3-pyridyl | 5-methyl-1-imidazolyl |
| 35 | 670 | F | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 671 | F | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 672 | F | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 673 | F | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 674 | F | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 40 | 675 | F | 2-pyrimidyl | 4-morpholino |
| | 676 | F | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 677 | F | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 678 | F | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 679 | F | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| 45 | 680 | F | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 681 | F | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 682 | F | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 683 | F | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 684 | F | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 50 | 685 | F | 5-pyrimidyl | 4-morpholino |
| | 686 | F | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 687 | F | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 688 | F | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 689 | F | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| 55 | 690 | F | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 691 | F | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |

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|----|-----|---------------------------------|----------------|---------------------------------------------|
| | 692 | F | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 693 | F | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 694 | F | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 695 | F | 2-Cl-phenyl | 4-morpholino |
| 5 | 696 | F | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 697 | F | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 698 | F | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 699 | F | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 700 | F | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 10 | 701 | F | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 702 | F | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 703 | F | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 704 | F | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 705 | F | 2-F-phenyl | 4-morpholino |
| 15 | 706 | F | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 707 | F | 2-F-phenyl | 4-morpholinocarbonyl |
| | 708 | F | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 709 | F | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 710 | F | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 20 | 711 | F | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 712 | F | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 713 | F | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 714 | F | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 715 | F | 2,6-diF-phenyl | 4-morpholino |
| 25 | 716 | F | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 717 | F | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 718 | F | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 719 | F | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 720 | F | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 30 | 721 | CO ₂ CH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| | 722 | CO ₂ CH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 723 | CO ₂ CH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 724 | CO ₂ CH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 725 | CO ₂ CH ₃ | phenyl | 4-morpholino |
| 35 | 726 | CO ₂ CH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 727 | CO ₂ CH ₃ | phenyl | 4-morpholinocarbonyl |
| | 728 | CO ₂ CH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 729 | CO ₂ CH ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 730 | CO ₂ CH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| 40 | 731 | CO ₂ CH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 732 | CO ₂ CH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 733 | CO ₂ CH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 734 | CO ₂ CH ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 735 | CO ₂ CH ₃ | 2-pyridyl | 4-morpholino |
| 45 | 736 | CO ₂ CH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 737 | CO ₂ CH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| | 738 | CO ₂ CH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 739 | CO ₂ CH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 740 | CO ₂ CH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| 50 | 741 | CO ₂ CH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 742 | CO ₂ CH ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 743 | CO ₂ CH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 744 | CO ₂ CH ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 745 | CO ₂ CH ₃ | 3-pyridyl | 4-morpholino |

| | | | | |
|----|-----|---------------------------------|----------------|---------------------------------------------|
| | 746 | CO ₂ CH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 747 | CO ₂ CH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| | 748 | CO ₂ CH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 749 | CO ₂ CH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| 5 | 750 | CO ₂ CH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 751 | CO ₂ CH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 752 | CO ₂ CH ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 753 | CO ₂ CH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 754 | CO ₂ CH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 10 | 755 | CO ₂ CH ₃ | 2-pyrimidyl | 4-morpholino |
| | 756 | CO ₂ CH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 757 | CO ₂ CH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 758 | CO ₂ CH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 759 | CO ₂ CH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| 15 | 760 | CO ₂ CH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 761 | CO ₂ CH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 762 | CO ₂ CH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 763 | CO ₂ CH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 764 | CO ₂ CH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| 20 | 765 | CO ₂ CH ₃ | 5-pyrimidyl | 4-morpholino |
| | 766 | CO ₂ CH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 767 | CO ₂ CH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 768 | CO ₂ CH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 769 | CO ₂ CH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| 25 | 770 | CO ₂ CH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 771 | CO ₂ CH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 772 | CO ₂ CH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 773 | CO ₂ CH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 774 | CO ₂ CH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| 30 | 775 | CO ₂ CH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 776 | CO ₂ CH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 777 | CO ₂ CH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 778 | CO ₂ CH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 779 | CO ₂ CH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| 35 | 780 | CO ₂ CH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 781 | CO ₂ CH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 782 | CO ₂ CH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 783 | CO ₂ CH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 784 | CO ₂ CH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| 40 | 785 | CO ₂ CH ₃ | 2-F-phenyl | 4-morpholino |
| | 786 | CO ₂ CH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 787 | CO ₂ CH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 788 | CO ₂ CH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 789 | CO ₂ CH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| 45 | 790 | CO ₂ CH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 791 | CO ₂ CH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 792 | CO ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 793 | CO ₂ CH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 794 | CO ₂ CH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| 50 | 795 | CO ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 796 | CO ₂ CH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 797 | CO ₂ CH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |

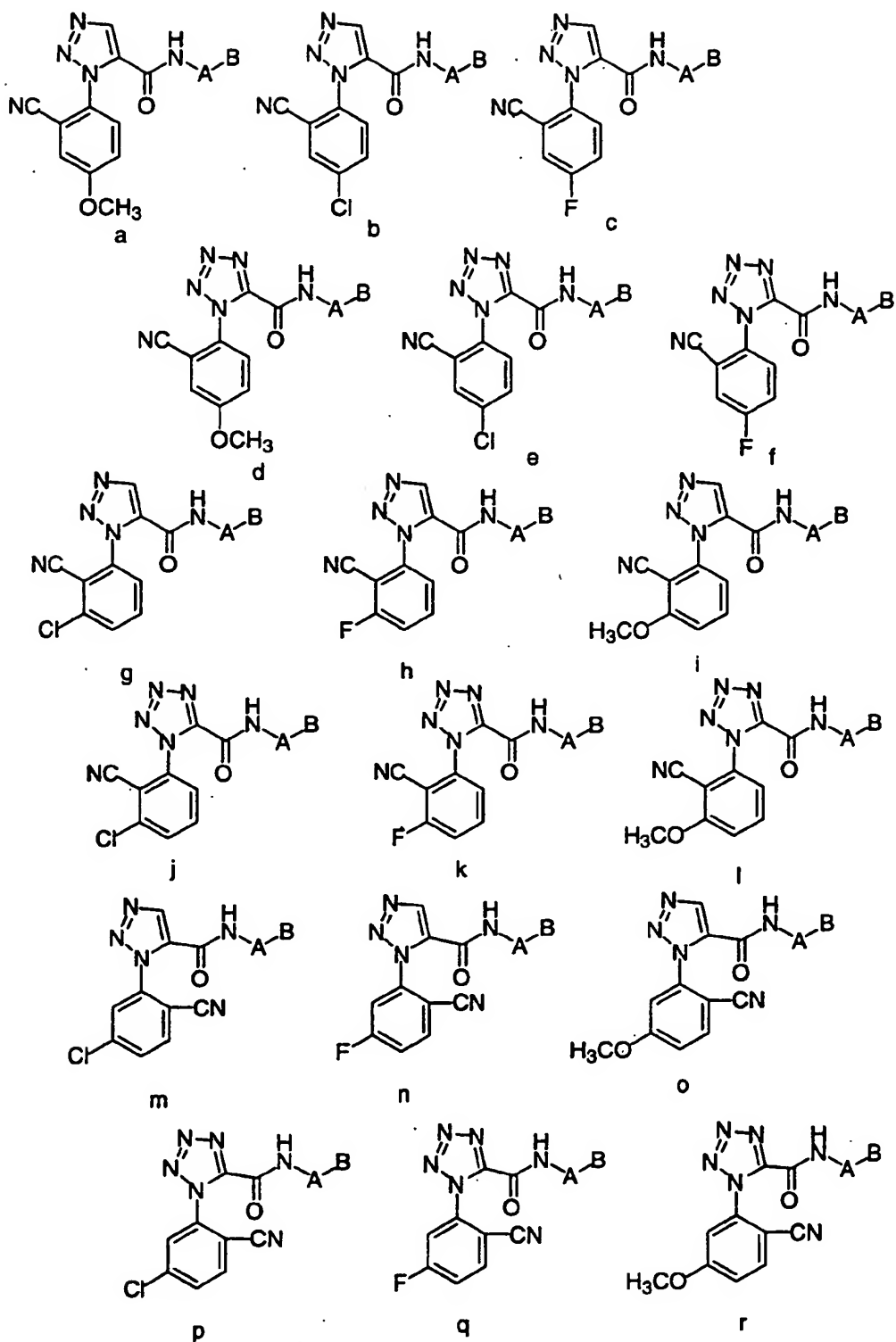
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|----|-----|----------------------------------|----------------|---------------------------------------------|
| | 798 | CO ₂ CH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 799 | CO ₂ CH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 800 | CO ₂ CH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 801 | CH ₂ OCH ₃ | phenyl | 2-(aminosulfonyl)phenyl |
| 5 | 802 | CH ₂ OCH ₃ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 803 | CH ₂ OCH ₃ | phenyl | 1-pyrrolidinocarbonyl |
| | 804 | CH ₂ OCH ₃ | phenyl | 2-(methylsulfonyl)phenyl |
| | 805 | CH ₂ OCH ₃ | phenyl | 4-morpholino |
| | 806 | CH ₂ OCH ₃ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 10 | 807 | CH ₂ OCH ₃ | phenyl | 4-morpholinocarbonyl |
| | 808 | CH ₂ OCH ₃ | phenyl | 2-methyl-1-imidazolyl |
| | 809 | CH ₂ OCH ₃ | phenyl | 5-methyl-1-imidazolyl |
| | 810 | CH ₂ OCH ₃ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 811 | CH ₂ OCH ₃ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| 15 | 812 | CH ₂ OCH ₃ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 813 | CH ₂ OCH ₃ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 814 | CH ₂ OCH ₃ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 815 | CH ₂ OCH ₃ | 2-pyridyl | 4-morpholino |
| | 816 | CH ₂ OCH ₃ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 20 | 817 | CH ₂ OCH ₃ | 2-pyridyl | 4-morpholinocarbonyl |
| | 818 | CH ₂ OCH ₃ | 2-pyridyl | 2-methyl-1-imidazolyl |
| | 819 | CH ₂ OCH ₃ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 820 | CH ₂ OCH ₃ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 821 | CH ₂ OCH ₃ | 3-pyridyl | 2-(aminosulfonyl)phenyl |
| 25 | 822 | CH ₂ OCH ₃ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 823 | CH ₂ OCH ₃ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 824 | CH ₂ OCH ₃ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 825 | CH ₂ OCH ₃ | 3-pyridyl | 4-morpholino |
| | 826 | CH ₂ OCH ₃ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 30 | 827 | CH ₂ OCH ₃ | 3-pyridyl | 4-morpholinocarbonyl |
| | 828 | CH ₂ OCH ₃ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 829 | CH ₂ OCH ₃ | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 830 | CH ₂ OCH ₃ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 831 | CH ₂ OCH ₃ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 35 | 832 | CH ₂ OCH ₃ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 833 | CH ₂ OCH ₃ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 834 | CH ₂ OCH ₃ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 835 | CH ₂ OCH ₃ | 2-pyrimidyl | 4-morpholino |
| | 836 | CH ₂ OCH ₃ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 40 | 837 | CH ₂ OCH ₃ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 838 | CH ₂ OCH ₃ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 839 | CH ₂ OCH ₃ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 840 | CH ₂ OCH ₃ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 841 | CH ₂ OCH ₃ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 45 | 842 | CH ₂ OCH ₃ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 843 | CH ₂ OCH ₃ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 844 | CH ₂ OCH ₃ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 845 | CH ₂ OCH ₃ | 5-pyrimidyl | 4-morpholino |
| | 846 | CH ₂ OCH ₃ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 50 | 847 | CH ₂ OCH ₃ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 848 | CH ₂ OCH ₃ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 849 | CH ₂ OCH ₃ | 5-pyrimidyl | 5-methyl-1-imidazolyl |

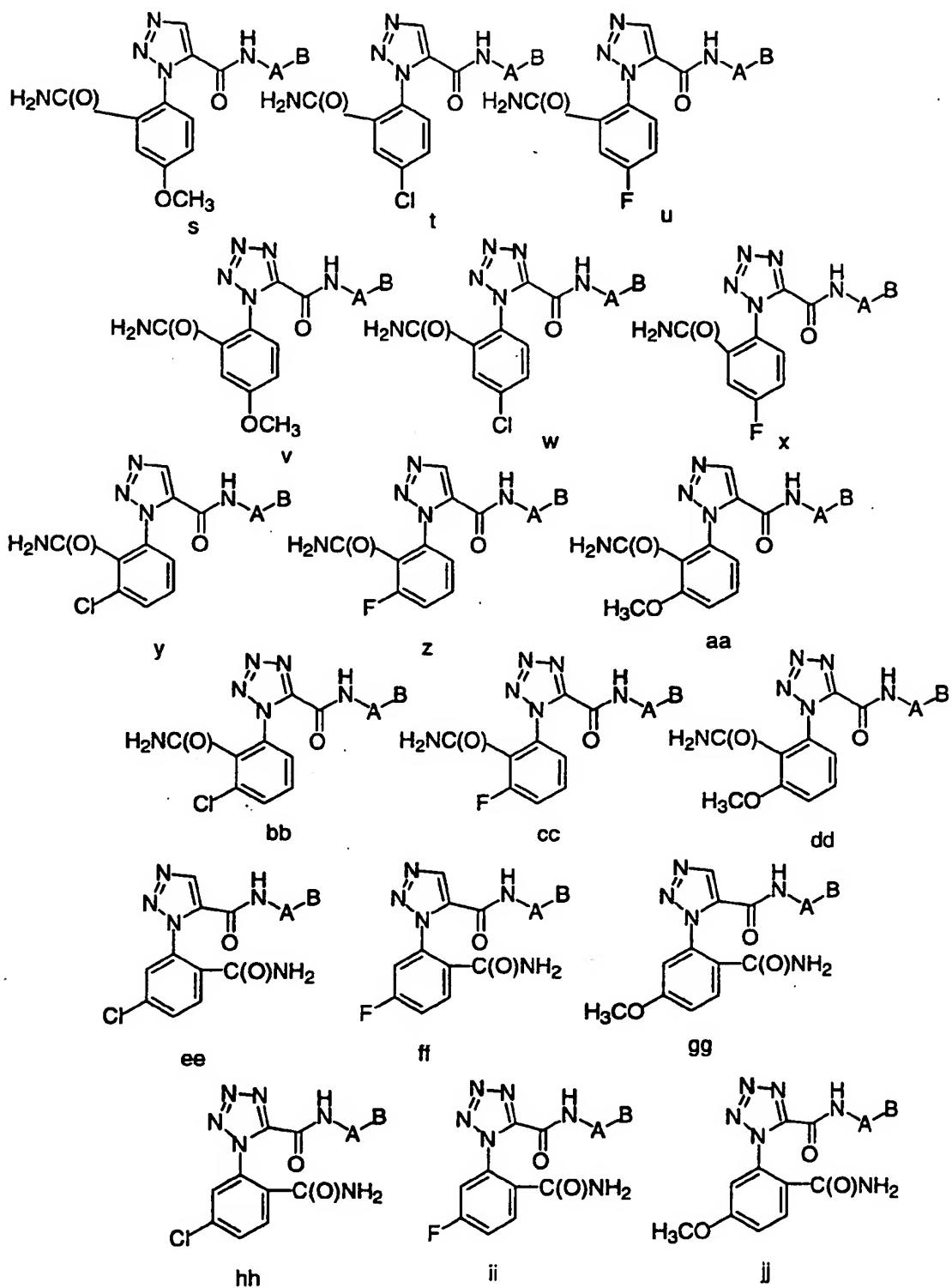
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|----|-----|----------------------------------|----------------|---------------------------------------------|
| | 850 | CH ₂ OCH ₃ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 851 | CH ₂ OCH ₃ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 852 | CH ₂ OCH ₃ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 853 | CH ₂ OCH ₃ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| 5 | 854 | CH ₂ OCH ₃ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 855 | CH ₂ OCH ₃ | 2-Cl-phenyl | 4-morpholino |
| | 856 | CH ₂ OCH ₃ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 857 | CH ₂ OCH ₃ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 858 | CH ₂ OCH ₃ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| 10 | 859 | CH ₂ OCH ₃ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 860 | CH ₂ OCH ₃ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 861 | CH ₂ OCH ₃ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 862 | CH ₂ OCH ₃ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 863 | CH ₂ OCH ₃ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| 15 | 864 | CH ₂ OCH ₃ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 865 | CH ₂ OCH ₃ | 2-F-phenyl | 4-morpholino |
| | 866 | CH ₂ OCH ₃ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 867 | CH ₂ OCH ₃ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 868 | CH ₂ OCH ₃ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| 20 | 869 | CH ₂ OCH ₃ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 870 | CH ₂ OCH ₃ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 871 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 872 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 873 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| 25 | 874 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 875 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 4-morpholino |
| | 876 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 877 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 878 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| 30 | 879 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 880 | CH ₂ OCH ₃ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 881 | CONH ₂ | phenyl | 2-(aminosulfonyl)phenyl |
| | 882 | CONH ₂ | phenyl | 2-(methylaminosulfonyl)phenyl |
| | 883 | CONH ₂ | phenyl | 1-pyrrolidinocarbonyl |
| 35 | 884 | CONH ₂ | phenyl | 2-(methylsulfonyl)phenyl |
| | 885 | CONH ₂ | phenyl | 4-morpholino |
| | 886 | CONH ₂ | phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 887 | CONH ₂ | phenyl | 4-morpholinocarbonyl |
| | 888 | CONH ₂ | phenyl | 2-methyl-1-imidazolyl |
| 40 | 889 | CONH ₂ | phenyl | 5-methyl-1-imidazolyl |
| | 890 | CONH ₂ | phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 891 | CONH ₂ | 2-pyridyl | 2-(aminosulfonyl)phenyl |
| | 892 | CONH ₂ | 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 893 | CONH ₂ | 2-pyridyl | 1-pyrrolidinocarbonyl |
| 45 | 894 | CONH ₂ | 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 895 | CONH ₂ | 2-pyridyl | 4-morpholino |
| | 896 | CONH ₂ | 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 897 | CONH ₂ | 2-pyridyl | 4-morpholinocarbonyl |
| | 898 | CONH ₂ | 2-pyridyl | 2-methyl-1-imidazolyl |
| 50 | 899 | CONH ₂ | 2-pyridyl | 5-methyl-1-imidazolyl |
| | 900 | CONH ₂ | 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 901 | CONH ₂ | 3-pyridyl | 2-(aminosulfonyl)phenyl |

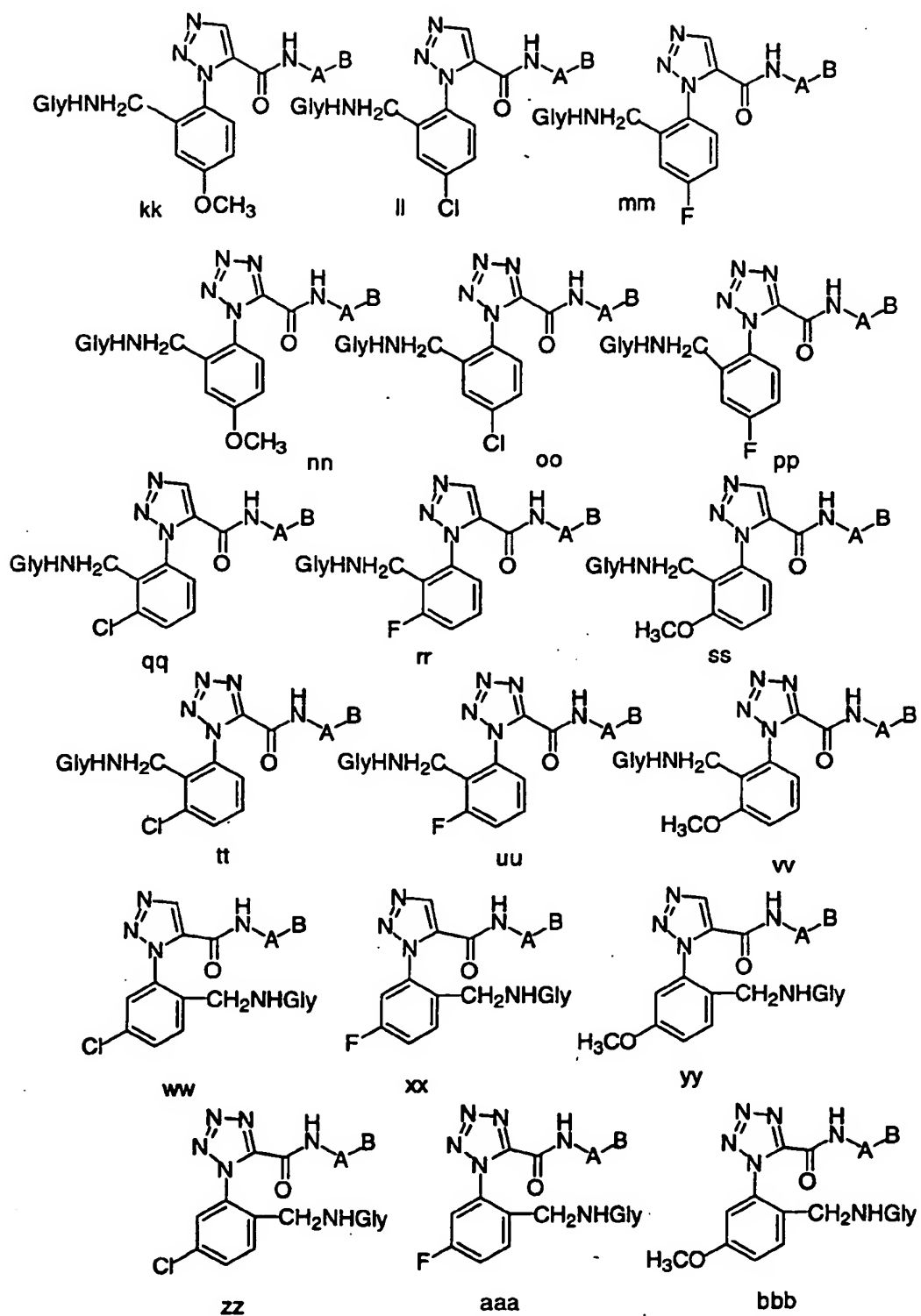
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|----|-----|-------------------|----------------|---------------------------------------------|
| | 902 | CONH ₂ | 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 903 | CONH ₂ | 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 904 | CONH ₂ | 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 905 | CONH ₂ | 3-pyridyl | 4-morpholino |
| 5 | 906 | CONH ₂ | 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 907 | CONH ₂ | 3-pyridyl | 4-morpholinocarbonyl |
| | 908 | CONH ₂ | 3-pyridyl | 2-methyl-1-imidazolyl |
| | 909 | CONH ₂ | 3-pyridyl | 5-methyl-1-imidazolyl |
| | 910 | CONH ₂ | 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| 10 | 911 | CONH ₂ | 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 912 | CONH ₂ | 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 913 | CONH ₂ | 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 914 | CONH ₂ | 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 915 | CONH ₂ | 2-pyrimidyl | 4-morpholino |
| 15 | 916 | CONH ₂ | 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 917 | CONH ₂ | 2-pyrimidyl | 4-morpholinocarbonyl |
| | 918 | CONH ₂ | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 919 | CONH ₂ | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 920 | CONH ₂ | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| 20 | 921 | CONH ₂ | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 922 | CONH ₂ | 5-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 923 | CONH ₂ | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 924 | CONH ₂ | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 925 | CONH ₂ | 5-pyrimidyl | 4-morpholino |
| 25 | 926 | CONH ₂ | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 927 | CONH ₂ | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 928 | CONH ₂ | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 929 | CONH ₂ | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 930 | CONH ₂ | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| 30 | 931 | CONH ₂ | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| | 932 | CONH ₂ | 2-Cl-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 933 | CONH ₂ | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 934 | CONH ₂ | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 935 | CONH ₂ | 2-Cl-phenyl | 4-morpholino |
| 35 | 936 | CONH ₂ | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 937 | CONH ₂ | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 938 | CONH ₂ | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 939 | CONH ₂ | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 940 | CONH ₂ | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 40 | 941 | CONH ₂ | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| | 942 | CONH ₂ | 2-F-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 943 | CONH ₂ | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 944 | CONH ₂ | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 945 | CONH ₂ | 2-F-phenyl | 4-morpholino |
| 45 | 946 | CONH ₂ | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 947 | CONH ₂ | 2-F-phenyl | 4-morpholinocarbonyl |
| | 948 | CONH ₂ | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 949 | CONH ₂ | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 950 | CONH ₂ | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| 50 | 951 | CONH ₂ | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| | 952 | CONH ₂ | 2,6-diF-phenyl | 2-(methylaminosulfonyl)phenyl |
| | 953 | CONH ₂ | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |

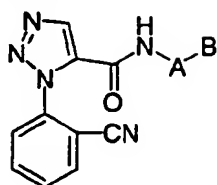
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|---|-----|-------------------|----------------|---------------------------------------------|
| | 954 | CONH ₂ | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 955 | CONH ₂ | 2,6-diF-phenyl | 4-morpholino |
| | 956 | CONH ₂ | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 957 | CONH ₂ | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| 5 | 958 | CONH ₂ | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 959 | CONH ₂ | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 960 | CONH ₂ | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |

Table 5

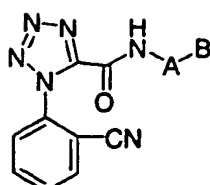




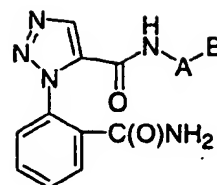




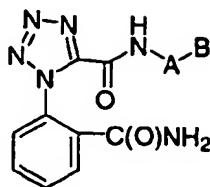
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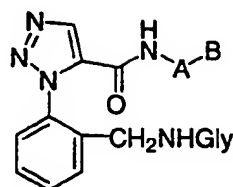
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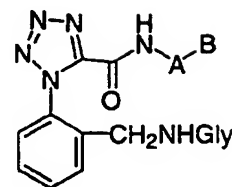
eee



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hhh

| Ex # | A | B |
|------|----------------|---------------------------------------------|
| 5 | 1 phenyl | 2-(aminosulfonyl)phenyl |
| | 2 phenyl | 2-(methylaminosulfonyl)phenyl |
| | 3 phenyl | 1-pyrrolidinocarbonyl |
| | 4 phenyl | 2-(methylsulfonyl)phenyl |
| | 5 phenyl | 4-morpholino |
| | 6 phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 10 | 7 phenyl | 4-morpholinocarbonyl |
| | 8 phenyl | 2-methyl-1-imidazolyl |
| | 9 phenyl | 5-methyl-1-imidazolyl |
| | 10 phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 11 2-pyridyl | 2-(aminosulfonyl)phenyl |
| 15 | 12 2-pyridyl | 2-(methylaminosulfonyl)phenyl |
| | 13 2-pyridyl | 1-pyrrolidinocarbonyl |
| | 14 2-pyridyl | 2-(methylsulfonyl)phenyl |
| | 15 2-pyridyl | 4-morpholino |
| | 16 2-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 17 2-pyridyl | 4-morpholinocarbonyl |
| 20 | 18 2-pyridyl | 2-methyl-1-imidazolyl |
| | 19 2-pyridyl | 5-methyl-1-imidazolyl |
| | 20 2-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 21 3-pyridyl | 2-(aminosulfonyl)phenyl |
| | 22 3-pyridyl | 2-(methylaminosulfonyl)phenyl |
| 25 | 23 3-pyridyl | 1-pyrrolidinocarbonyl |
| | 24 3-pyridyl | 2-(methylsulfonyl)phenyl |
| | 25 3-pyridyl | 4-morpholino |
| | 26 3-pyridyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 27 3-pyridyl | 4-morpholinocarbonyl |
| | 28 3-pyridyl | 2-methyl-1-imidazolyl |
| 30 | 29 3-pyridyl | 5-methyl-1-imidazolyl |
| | 30 3-pyridyl | 2-methylsulfonyl-1-imidazolyl |
| | 31 2-pyrimidyl | 2-(aminosulfonyl)phenyl |
| | 32 2-pyrimidyl | 2-(methylaminosulfonyl)phenyl |
| | 33 2-pyrimidyl | 1-pyrrolidinocarbonyl |
| 35 | 34 2-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 35 2-pyrimidyl | 4-morpholino |
| | 36 2-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| | 37 2-pyrimidyl | 4-morpholinocarbonyl |

| | | | |
|----|----|----------------|---------------------------------------------|
| | 38 | 2-pyrimidyl | 2-methyl-1-imidazolyl |
| | 39 | 2-pyrimidyl | 5-methyl-1-imidazolyl |
| | 40 | 2-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 41 | 5-pyrimidyl | 2-(aminosulfonyl)phenyl |
| 5 | 42 | 5-pyrimidyl | 2-(methyaminosulfonyl)phenyl |
| | 43 | 5-pyrimidyl | 1-pyrrolidinocarbonyl |
| | 44 | 5-pyrimidyl | 2-(methylsulfonyl)phenyl |
| | 45 | 5-pyrimidyl | 4-morpholino |
| | 46 | 5-pyrimidyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 10 | 47 | 5-pyrimidyl | 4-morpholinocarbonyl |
| | 48 | 5-pyrimidyl | 2-methyl-1-imidazolyl |
| | 49 | 5-pyrimidyl | 5-methyl-1-imidazolyl |
| | 50 | 5-pyrimidyl | 2-methylsulfonyl-1-imidazolyl |
| | 51 | 2-Cl-phenyl | 2-(aminosulfonyl)phenyl |
| 15 | 52 | 2-Cl-phenyl | 2-(methyaminosulfonyl)phenyl |
| | 53 | 2-Cl-phenyl | 1-pyrrolidinocarbonyl |
| | 54 | 2-Cl-phenyl | 2-(methylsulfonyl)phenyl |
| | 55 | 2-Cl-phenyl | 4-morpholino |
| | 56 | 2-Cl-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 20 | 57 | 2-Cl-phenyl | 4-morpholinocarbonyl |
| | 58 | 2-Cl-phenyl | 2-methyl-1-imidazolyl |
| | 59 | 2-Cl-phenyl | 5-methyl-1-imidazolyl |
| | 60 | 2-Cl-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 61 | 2-F-phenyl | 2-(aminosulfonyl)phenyl |
| 25 | 62 | 2-F-phenyl | 2-(methyaminosulfonyl)phenyl |
| | 63 | 2-F-phenyl | 1-pyrrolidinocarbonyl |
| | 64 | 2-F-phenyl | 2-(methylsulfonyl)phenyl |
| | 65 | 2-F-phenyl | 4-morpholino |
| | 66 | 2-F-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 30 | 67 | 2-F-phenyl | 4-morpholinocarbonyl |
| | 68 | 2-F-phenyl | 2-methyl-1-imidazolyl |
| | 69 | 2-F-phenyl | 5-methyl-1-imidazolyl |
| | 70 | 2-F-phenyl | 2-methylsulfonyl-1-imidazolyl |
| | 71 | 2,6-diF-phenyl | 2-(aminosulfonyl)phenyl |
| 35 | 72 | 2,6-diF-phenyl | 2-(methyaminosulfonyl)phenyl |
| | 73 | 2,6-diF-phenyl | 1-pyrrolidinocarbonyl |
| | 74 | 2,6-diF-phenyl | 2-(methylsulfonyl)phenyl |
| | 75 | 2,6-diF-phenyl | 4-morpholino |
| | 76 | 2,6-diF-phenyl | 2-(1'-CF ₃ -tetrazol-2-yl)phenyl |
| 40 | 77 | 2,6-diF-phenyl | 4-morpholinocarbonyl |
| | 78 | 2,6-diF-phenyl | 2-methyl-1-imidazolyl |
| | 79 | 2,6-diF-phenyl | 5-methyl-1-imidazolyl |
| | 80 | 2,6-diF-phenyl | 2-methylsulfonyl-1-imidazolyl |

Utility

The compounds of this invention are useful as anticoagulants for the treatment or prevention of thromboembolic disorders in mammals. The term "thromboembolic disorders" as used herein includes arterial or venous cardiovascular or cerebrovascular thromboembolic disorders, including, for example, unstable angina, first or recurrent myocardial infarction, ischemic sudden death, transient ischemic attack, stroke, atherosclerosis, venous thrombosis, deep vein thrombosis, thrombophlebitis, arterial embolism, coronary and cerebral arterial thrombosis, cerebral embolism, kidney embolisms, and pulmonary embolisms. The anticoagulant effect of compounds of the present invention is believed to be due to inhibition of factor Xa or thrombin.

The effectiveness of compounds of the present invention as inhibitors of factor Xa was determined using purified human factor Xa and synthetic substrate. The rate of factor Xa hydrolysis of chromogenic substrate S2222 (Kabi Pharmacia, Franklin, OH) was measured both in the absence and presence of compounds of the present invention. Hydrolysis of the substrate resulted in the release of pNA, which was monitored spectrophotometrically by measuring the increase in absorbance at 405 nm. A decrease in the rate of absorbance change at 405 nm in the presence of inhibitor is indicative of enzyme inhibition. The results of this assay are expressed as inhibitory constant, K_i .

Factor Xa determinations were made in 0.10 M sodium phosphate buffer, pH 7.5, containing 0.20 M NaCl, and 0.5 % PEG 8000. The Michaelis constant, K_m , for substrate hydrolysis was determined at 25°C using the method of Lineweaver and Burk. Values of K_i were determined by allowing 0.2-0.5 nM human factor Xa (Enzyme Research Laboratories, South Bend, IN) to react with the substrate (0.20 mM-1 mM) in the presence of inhibitor. Reactions were allowed to go for 30 minutes and the velocities (rate of absorbance change vs time) were measured in the time frame of 25-30 minutes. The following relationship was used to calculate K_i values:

$$(v_o - v_s) / v_s = I / (K_i (1 + S / K_m))$$

where:

v_0 is the velocity of the control in the absence of inhibitor;

v_s is the velocity in the presence of inhibitor;

5 I is the concentration of inhibitor;

K_i is the dissociation constant of the enzyme:inhibitor complex;

S is the concentration of substrate;

K_m is the Michaelis constant.

10 Using the methodology described above, a number of compounds of the present invention were found to exhibit a K_i of $\leq 10 \mu M$, thereby confirming the utility of the compounds of the present invention as effective Xa inhibitors.

The antithrombotic effect of compounds of the present
15 invention can be demonstrated in a rabbit arterio-venous (AV) shunt thrombosis model. In this model, rabbits weighing 2-3 kg anesthetized with a mixture of xylazine (10 mg/kg i.m.) and ketamine (50 mg/kg i.m.) are used. A saline-filled AV shunt device is connected between the femoral arterial and the
20 femoral venous cannulae. The AV shunt device consists of a piece of 6-cm tygon tubing which contains a piece of silk thread. Blood will flow from the femoral artery via the AV-shunt into the femoral vein. The exposure of flowing blood to a silk thread will induce the formation of a significant
25 thrombus. After forty minutes, the shunt is disconnected and the silk thread covered with thrombus is weighed. Test agents or vehicle will be given (i.v., i.p., s.c., or orally) prior to the opening of the AV shunt. The percentage inhibition of thrombus formation is determined for each treatment group.
30 The ID50 values (dose which produces 50% inhibition of thrombus formation) are estimated by linear regression.

The compounds of formula (I) may also be useful as inhibitors of serine proteases, notably human thrombin, plasma kallikrein and plasmin. Because of their inhibitory action,
35 these compounds are indicated for use in the prevention or treatment of physiological reactions, blood coagulation and inflammation, catalyzed by the aforesaid class of enzymes. Specifically, the compounds have utility as drugs for the

treatment of diseases arising from elevated thrombin activity such as myocardial infarction, and as reagents used as anticoagulants in the processing of blood to plasma for diagnostic and other commercial purposes.

5 Some compounds of the present invention were shown to be direct acting inhibitors of the serine protease thrombin by their ability to inhibit the cleavage of small molecule substrates by thrombin in a purified system. *In vitro* inhibition constants were determined by the method described
10 by Kettner et al. in *J. Biol. Chem.* **265**, 18289-18297 (1990), herein incorporated by reference. In these assays, thrombin-mediated hydrolysis of the chromogenic substrate S2238 (Helena Laboratories, Beaumont, TX) was monitored spectrophotometrically. Addition of an inhibitor to the assay
15 mixture results in decreased absorbance and is indicative of thrombin inhibition. Human thrombin (Enzyme Research Laboratories, Inc., South Bend, IN) at a concentration of 0.2 nM in 0.10 M sodium phosphate buffer, pH 7.5, 0.20 M NaCl, and 0.5% PEG 6000, was incubated with various substrate
20 concentrations ranging from 0.20 to 0.02 mM. After 25 to 30 minutes of incubation, thrombin activity was assayed by monitoring the rate of increase in absorbance at 405 nm which arises owing to substrate hydrolysis. Inhibition constants were derived from reciprocal plots of the reaction velocity as
25 a function of substrate concentration using the standard method of Lineweaver and Burk. Using the methodology described above, some compounds of this invention were evaluated and found to exhibit a K_i of less than 10 μ M, thereby confirming the utility of the compounds of the present
30 invention as effective thrombin inhibitors.

The compounds of the present invention can be administered alone or in combination with one or more additional therapeutic agents. These include other anti-coagulant or coagulation inhibitory agents, anti-platelet or
35 platelet inhibitory agents, thrombin inhibitors, or thrombolytic or fibrinolytic agents.

The compounds are administered to a mammal in a therapeutically effective amount. By "therapeutically

effective amount" it is meant an amount of a compound of Formula I that, when administered alone or in combination with an additional therapeutic agent to a mammal, is effective to prevent or ameliorate the thromboembolic disease condition or the progression of the disease.

By "administered in combination" or "combination therapy" it is meant that the compound of Formula I and one or more additional therapeutic agents are administered concurrently to the mammal being treated. When administered in combination each component may be administered at the same time or sequentially in any order at different points in time. Thus, each component may be administered separately but sufficiently closely in time so as to provide the desired therapeutic effect. Other anticoagulant agents (or coagulation inhibitory agents) that may be used in combination with the compounds of this invention include warfarin and heparin, as well as other factor Xa inhibitors such as those described in the publications identified above under Background of the Invention.

The term anti-platelet agents (or platelet inhibitory agents), as used herein, denotes agents that inhibit platelet function such as by inhibiting the aggregation, adhesion or granular secretion of platelets. Such agents include, but are not limited to, the various known non-steroidal anti-inflammatory drugs (NSAIDS) such as aspirin, ibuprofen, naproxen, sulindac, indomethacin, mefenamate, droxicam, diclofenac, sulfinpyrazone, and piroxicam, including pharmaceutically acceptable salts or prodrugs thereof. Of the NSAIDS, aspirin (acetylsalicyclic acid or ASA), and piroxicam are preferred. Other suitable anti-platelet agents include ticlopidine, including pharmaceutically acceptable salts or prodrugs thereof. Ticlopidine is also a preferred compound since it is known to be gentle on the gastro-intestinal tract in use. Still other suitable platelet inhibitory agents include IIb/IIIa antagonists, thromboxane-A₂-receptor antagonists and thromboxane-A₂-synthetase inhibitors, as well as pharmaceutically acceptable salts or prodrugs thereof.

The term thrombin inhibitors (or anti-thrombin agents), as used herein, denotes inhibitors of the serine protease thrombin. By inhibiting thrombin, various thrombin-mediated processes, such as thrombin-mediated platelet activation (that is, for example, the aggregation of platelets, and/or the granular secretion of plasminogen activator inhibitor-1 and/or serotonin) and/or fibrin formation are disrupted. A number of thrombin inhibitors are known to one of skill in the art and these inhibitors are contemplated to be used in combination with the present compounds. Such inhibitors include, but are not limited to, boroarginine derivatives, boro peptides, heparins, hirudin and argatroban, including pharmaceutically acceptable salts and prodrugs thereof. Boroarginine derivatives and boro peptides include N-acetyl and peptide derivatives of boronic acid, such as C-terminal α -aminoboronic acid derivatives of lysine, ornithine, arginine, homoarginine and corresponding isothiuronium analogs thereof. The term hirudin, as used herein, includes suitable derivatives or analogs of hirudin, referred to herein as hirulogs, such as disulfatohirudin. Boro peptide thrombin inhibitors include compounds described in Kettner et al., U.S. Patent No. 5,187,157 and European Patent Application Publication Number 293 881 A2, the disclosures of which are hereby incorporated herein by reference. Other suitable boroarginine derivatives and boro peptide thrombin inhibitors include those disclosed in PCT Application Publication Number 92/07869 and European Patent Application Publication Number 471,651 A2, the disclosures of which are hereby incorporated herein by reference.

The term thrombolytics (or fibrinolytic) agents (or thrombolytics or fibrinolytics), as used herein, denotes agents that lyse blood clots (thrombi). Such agents include tissue plasminogen activator, anistreplase, urokinase or streptokinase, including pharmaceutically acceptable salts or prodrugs thereof. The term anistreplase, as used herein, refers to anisoylated plasminogen streptokinase activator complex, as described, for example, in European Patent Application No. 028,489, the disclosure of which is hereby

incorporated herein by reference herein. The term urokinase, as used herein, is intended to denote both dual and single chain urokinase, the latter also being referred to herein as prourokinase.

5 Administration of the compounds of Formula I of the invention in combination with such additional therapeutic agent, may afford an efficacy advantage over the compounds and agents alone, and may do so while permitting the use of lower doses of each. A lower dosage minimizes the potential of side
10 effects, thereby providing an increased margin of safety.

The compounds of the present invention are also useful as standard or reference compounds, for example as a quality standard or control, in tests or assays involving the inhibition of factor Xa. Such compounds may be provided in a
15 commercial kit, for example, for use in pharmaceutical research involving factor Xa. For example, a compound of the present invention could be used as a reference in an assay to compare its known activity to a compound with an unknown activity. This would ensure the experimenter that the assay
20 was being performed properly and provide a basis for comparison, especially if the test compound was a derivative of the reference compound. When developing new assays or protocols, compounds according to the present invention could be used to test their effectiveness.

25 The compounds of the present invention may also be used in diagnostic assays involving factor Xa. For example, the presence of factor Xa in an unknown sample could be determined by addition of chromogenic substrate S2222 to a series of solutions containing test sample and optionally one of the
30 compounds of the present invention. If production of pNA is observed in the solutions containing test sample, but not in the presence of a compound of the present invention, then one would conclude factor Xa was present.

35 Dosage and Formulation

The compounds of this invention can be administered in such oral dosage forms as tablets, capsules (each of which includes sustained release or timed release formulations),

pills, powders, granules, elixirs, tinctures, suspensions, syrups, and emulsions. They may also be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using dosage forms well known to those of ordinary skill in the pharmaceutical arts. They can be administered alone, but generally will be administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice.

10 The dosage regimen for the compounds of the present invention will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the species, age, sex, health, medical condition, and weight of the
15 recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; the route of administration, the renal and hepatic function of the patient, and the effect desired. A physician or veterinarian can determine and prescribe the effective amount of the drug
20 required to prevent, counter, or arrest the progress of the thromboembolic disorder.

 By way of general guidance, the daily oral dosage of each active ingredient, when used for the indicated effects, will range between about 0.001 to 1000 mg/kg of body weight, preferably between about 0.01 to 100 mg/kg of body weight per
25 day, and most preferably between about 1.0 to 20 mg/kg/day. Intravenously, the most preferred doses will range from about 1 to about 10 mg/kg/minute during a constant rate infusion. Compounds of this invention may be administered in a single
30 daily dose, or the total daily dosage may be administered in divided doses of two, three, or four times daily.

 Compounds of this invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal skin
35 patches. When administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen.

The compounds are typically administered in admixture with suitable pharmaceutical diluents, excipients, or carriers (collectively referred to herein as pharmaceutical carriers) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixirs, syrups and the like, and consistent with conventional pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water, and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents, and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth, or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum, and the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

Compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol,

polyhydroxyethylaspartamidophenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled
5 release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihdropyrans, polycyanoacylates, and crosslinked or amphipathic block
10 copolymers of hydrogels.

Dosage forms (pharmaceutical compositions) suitable for administration may contain from about 1 milligram to about 100 milligrams of active ingredient per dosage unit. In these pharmaceutical compositions the active ingredient will
15 ordinarily be present in an amount of about 0.5-95% by weight based on the total weight of the composition.

Gelatin capsules may contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like.
20 Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the
25 tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Liquid dosage forms for oral administration can contain coloring and flavoring to increase patient acceptance.

In general, water, a suitable oil, saline, aqueous
30 dextrose (glucose), and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are suitable carriers for parenteral solutions. Solutions for parenteral administration preferably contain a water soluble salt of the active ingredient, suitable stabilizing agents, and if
35 necessary, buffer substances. Antioxidizing agents such as sodium bisulfite, sodium sulfite, or ascorbic acid, either alone or combined, are suitable stabilizing agents. Also used are citric acid and its salts and sodium EDTA. In addition,

parenteral solutions can contain preservatives, such as benzalkonium chloride, methyl- or propyl-paraben, and chlorobutanol.

Suitable pharmaceutical carriers are described in
5 Remington's Pharmaceutical Sciences, Mack Publishing Company, a standard reference text in this field.

Representative useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

10 Capsules

A large number of unit capsules can be prepared by filling standard two-piece hard gelatin capsules each with 100 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams
15 magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestable oil such as soybean oil, cottonseed oil or olive oil may be prepared and injected by means of a positive displacement pump into
20 gelatin to form soft gelatin capsules containing 100 milligrams of the active ingredient. The capsules should be washed and dried.

Tablets

Tablets may be prepared by conventional procedures so
25 that the dosage unit is 100 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase
30 palatability or delay absorption.

Injectable

A parenteral composition suitable for administration by injection may be prepared by stirring 1.5% by weight of active ingredient in 10% by volume propylene glycol and water. The
35 solution should be made isotonic with sodium chloride and sterilized.

Suspension

An aqueous suspension can be prepared for oral administration so that each 5 mL contain 100 mg of finely divided active ingredient, 200 mg of sodium carboxymethyl
5 cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution, U.S.P., and 0.025 mL of vanillin.

Where the compounds of this invention are combined with other anticoagulant agents, for example, a daily dosage may be about 0.1 to 100 milligrams of the compound of Formula I and
10 about 1 to 7.5 milligrams of the second anticoagulant, per kilogram of patient body weight. For a tablet dosage form, the compounds of this invention generally may be present in an amount of about 5 to 10 milligrams per dosage unit, and the second anti-coagulant in an amount of about 1 to 5 milligrams
15 per dosage unit.

Where the compounds of Formula I are administered in combination with an anti-platelet agent, by way of general guidance, typically a daily dosage may be about 0.01 to 25 milligrams of the compound of Formula I and about 50 to 150
20 milligrams of the anti-platelet agent, preferably about 0.1 to 1 milligrams of the compound of Formula I and about 1 to 3 milligrams of antiplatelet agents, per kilogram of patient body weight.

Where the compounds of Formula I are administered in
25 combination with thrombolytic agent, typically a daily dosage may be about 0.1 to 1 milligrams of the compound of Formula I, per kilogram of patient body weight and, in the case of the thrombolytic agents, the usual dosage of the thrombolytic agent when administered alone may be reduced by about 70-80% when
30 administered with a compound of Formula I.

Where two or more of the foregoing second therapeutic agents are administered with the compound of Formula I, generally the amount of each component in a typical daily dosage and typical dosage form may be reduced relative to the
35 usual dosage of the agent when administered alone, in view of the additive or synergistic effect of the therapeutic agents when administered in combination.

Particularly when provided as a single dosage unit, the potential exists for a chemical interaction between the combined active ingredients. For this reason, when the compound of Formula I and a second therapeutic agent are combined in a single dosage unit they are formulated such that although the active ingredients are combined in a single dosage unit, the physical contact between the active ingredients is minimized (that is, reduced). For example, one active ingredient may be enteric coated. By enteric coating one of the active ingredients, it is possible not only to minimize the contact between the combined active ingredients, but also, it is possible to control the release of one of these components in the gastrointestinal tract such that one of these components is not released in the stomach but rather is released in the intestines. One of the active ingredients may also be coated with a material which effects a sustained-release throughout the gastrointestinal tract and also serves to minimize physical contact between the combined active ingredients. Furthermore, the sustained-released component can be additionally enteric coated such that the release of this component occurs only in the intestine. Still another approach would involve the formulation of a combination product in which the one component is coated with a sustained and/or enteric release polymer, and the other component is also coated with a polymer such as a lowviscosity grade of hydroxypropyl methylcellulose (HPMC) or other appropriate materials as known in the art, in order to further separate the active components. The polymer coating serves to form an additional barrier to interaction with the other component.

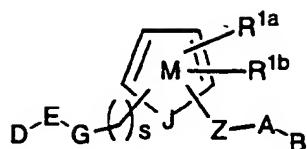
These as well as other ways of minimizing contact between the components of combination products of the present invention, whether administered in a single dosage form or administered in separate forms but at the same time by the same manner, will be readily apparent to those skilled in the art, once armed with the present disclosure.

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the

scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

WHAT IS CLAIMED IS:

1. A compound of formula I:



I

or a stereoisomer or pharmaceutically acceptable salt thereof,
wherein;

- 10 ring M contains, in addition to J, 0-3 N atoms, provided that
if M contains 2 N atoms then R^{1b} is not present and if M
contains 3 N atoms then R^{1a} and R^{1b} are not present;

J is N or NH;

15

D is selected from CN, C(=NR⁸)NR⁷R⁹, NHC(=NR⁸)NR⁷R⁹,
NR⁸CH(=NR⁷), C(O)NR⁷R⁸, and (CR⁸R⁹)_tNR⁷R⁸, provided that D
is substituted ortho to G on E;

- 20 E is selected from phenyl, pyridyl, pyrimidyl, pyrazinyl,
pyridazinyl, and piperidinyI substituted with 1-2 R;

R is selected from H, Cl, F, Br, I, (CH₂)_tOR³, C₁₋₄ alkyl,
OCF₃, CF₃, C(O)NR⁷R⁸, and (CR⁸R⁹)_tNR⁷R⁸;

25

G is absent or is selected from NHCH₂, OCH₂, and SCH₂, provided
that when s is 0, then G is attached to a carbon atom on
ring M;

- 30 Z is selected from a C₁₋₄ alkylene, (CH₂)_rO(CH₂)_r,
(CH₂)_rNR³(CH₂)_r, (CH₂)_rC(O)(CH₂)_r, (CH₂)_rC(O)O(CH₂)_r,
(CH₂)_rOC(O)(CH₂)_r, (CH₂)_rC(O)NR³(CH₂)_r,
(CH₂)_rNR³C(O)(CH₂)_r, (CH₂)_rOC(O)O(CH₂)_r,
(CH₂)_rOC(O)NR³(CH₂)_r, (CH₂)_rNR³C(O)O(CH₂)_r,
35 (CH₂)_rNR³C(O)NR³(CH₂)_r, (CH₂)_rS(O)_p(CH₂)_r,

$(\text{CH}_2)_r\text{SO}_2\text{NR}^3(\text{CH}_2)_r$, $(\text{CH}_2)_r\text{NR}^3\text{SO}_2(\text{CH}_2)_r$, and $(\text{CH}_2)_r\text{NR}^3\text{SO}_2\text{NR}^3(\text{CH}_2)_r$, provided that Z does not form a N-N, N-O, N-S, NCH_2N , NCH_2O , or NCH_2S bond with ring M or group A;

5

R^{1a} and R^{1b} are independently absent or selected from $-(\text{CH}_2)_r\text{R}^{1'}$, $-\text{CH}=\text{CH}-\text{R}^{1'}$, $\text{NCH}_2\text{R}^{1''}$, $\text{OCH}_2\text{R}^{1''}$, $\text{SCH}_2\text{R}^{1''}$, $\text{NH}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$, $\text{O}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$, and $\text{S}(\text{CH}_2)_2(\text{CH}_2)_t\text{R}^{1'}$;

10 alternatively, R^{1a} and R^{1b} , when attached to adjacent carbon atoms, together with the atoms to which they are attached form a 5-8 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^4 and which contains from 0-2 heteroatoms selected from the group
15 consisting of N, O, and S;

$\text{R}^{1'}$ is selected from H, C_{1-3} alkyl, F, Cl, Br, I, $-\text{CN}$, $-\text{CHO}$, $(\text{CF}_2)_r\text{CF}_3$, $(\text{CH}_2)_r\text{OR}^2$, NR^2R^{2a} , $\text{C}(\text{O})\text{R}^{2c}$, $\text{OC}(\text{O})\text{R}^2$, $(\text{CF}_2)_r\text{CO}_2\text{R}^{2c}$, $\text{S}(\text{O})_p\text{R}^{2b}$, $\text{NR}^2(\text{CH}_2)_r\text{OR}^2$, $\text{CH}(=\text{NR}^{2c})\text{NR}^2\text{R}^{2a}$,
20 $\text{NR}^2\text{C}(\text{O})\text{R}^{2b}$, $\text{NR}^2\text{C}(\text{O})\text{NHR}^{2b}$, $\text{NR}^2\text{C}(\text{O})_2\text{R}^{2a}$, $\text{OC}(\text{O})\text{NR}^{2a}\text{R}^{2b}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{C}(\text{O})\text{NR}^2(\text{CH}_2)_r\text{OR}^2$, $\text{SO}_2\text{NR}^2\text{R}^{2a}$, $\text{NR}^2\text{SO}_2\text{R}^{2b}$, C_{3-6} carbocyclic residue substituted with 0-2 R^4 , and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O,
25 and S substituted with 0-2 R^4 ;

$\text{R}^{1''}$ is selected from H, $\text{CH}(\text{CH}_2\text{OR}^2)_2$, $\text{C}(\text{O})\text{R}^{2c}$, $\text{C}(\text{O})\text{NR}^2\text{R}^{2a}$, $\text{S}(\text{O})\text{R}^{2b}$, $\text{S}(\text{O})_2\text{R}^{2b}$, and $\text{SO}_2\text{NR}^2\text{R}^{2a}$;

30 R^2 , at each occurrence, is selected from H, CF_3 , C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b} , and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b} ;

35

R^{2a} , at each occurrence, is selected from H, CF_3 , C_{1-6} alkyl, benzyl, C_{3-6} carbocyclic residue substituted with 0-2 R^{4b} , and 5-6 membered heterocyclic system containing from 1-4

heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

5 R^{2b}, at each occurrence, is selected from CF₃, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

10 R^{2c}, at each occurrence, is selected from CF₃, OH, C₁₋₄ alkoxy, C₁₋₆ alkyl, benzyl, C₃₋₆ carbocyclic residue substituted with 0-2 R^{4b}, and 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4b};

15 alternatively, R² and R^{2a} combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} which contains from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

20 alternatively, R² and R^{2a}, together with the atom to which they are attached, combine to form a 5 or 6 membered saturated, partially saturated or unsaturated ring substituted with 0-2 R^{4b} and containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

30 R³, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3a}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

35 R^{3b}, at each occurrence, is selected from H, C₁₋₄ alkyl, and phenyl;

R^{3c}, at each occurrence, is selected from C₁₋₄ alkyl, and phenyl;

A is selected from:

- 5 C₃₋₁₀ carbocyclic residue substituted with 0-2 R⁴, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R⁴;

- 10 B is selected from:

X-Y, NR²R^{2a}, C(=NR²)NR²R^{2a}, NR²C(=NR²)NR²R^{2a}, C₃₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

X is selected from C₁₋₄ alkylene, -CR²(CR²R^{2b})(CH₂)_t-, -C(O)-, -C(=NR^{1'})-, -CR²(NR^{1'}R²)-, -CR²(OR²)-, -CR²(SR²)-, -C(O)CR²R^{2a}-, -CR²R^{2a}C(O)-, -S(O)_p-, -S(O)_pCR²R^{2a}-, -CR²R^{2a}S(O)_p-, -S(O)₂NR²-, -NR²S(O)₂-, -NR²S(O)₂CR²R^{2a}-, -CR²R^{2a}S(O)₂NR²-, -NR²S(O)₂NR²-, -C(O)NR²-, -NR²C(O)-, -C(O)NR²CR²R^{2a}-, -NR²C(O)CR²R^{2a}-, -CR²R^{2a}C(O)NR²-, -CR²R^{2a}NR²C(O)-, -NR²C(O)O-, -OC(O)NR²-, -NR²C(O)NR²-, -NR²-, -NR²CR²R^{2a}-, -CR²R^{2a}NR²-, O, -CR²R^{2a}O-, and -OCR²R^{2a}-;

Y is selected from:

- (CH₂)_rNR²R^{2a}, provided that X-Y do not form a N-N, O-N, or S-N bond,
- 30 C₃₋₁₀ carbocyclic residue substituted with 0-2 R^{4a}, and 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-2 R^{4a};

- 35 R⁴, at each occurrence, is selected from H, =O, (CH₂)_rOR², F, Cl, Br, I, C₁₋₄ alkyl, -CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2c}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, NR²C(O)NR²R^{2a}, CH(=NR²)NR²R^{2a}, CH(=NS(O)₂R⁵)NR²R^{2a}, NHC(=NR²)NR²R^{2a},

$C(O)NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, $(CF_2)_rCF_3$, $NCH_2R^{1'}$, $OCH_2R^{1'}$, $SCH_2R^{1'}$, $N(CH_2)_2(CH_2)_tR^{1'}$, $O(CH_2)_2(CH_2)_tR^{1'}$, and $S(CH_2)_2(CH_2)_tR^{1'}$,

5

alternatively, one R^4 is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

- 10 R^{4a} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^2$, $(CH_2)_r-F$, $(CH_2)_r-Br$, $(CH_2)_r-Cl$, Cl, Br, F, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2c}$, $NR^2C(O)R^{2b}$, $C(O)NR^2R^{2a}$, $C(O)NH(CH_2)_2NR^2R^{2a}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NR^2)NR^2R^{2a}$, $NHC(=NR^2)NR^2R^{2a}$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, $NR^2SO_2-C_{1-4}$ alkyl, $C(O)NHSO_2-C_{1-4}$ alkyl, $NR^2SO_2R^5$, $S(O)_pR^5$, and $(CF_2)_rCF_3$;
- 15

alternatively, one R^{4a} is a 5-6 membered aromatic heterocycle containing from 1-4 heteroatoms selected from the group consisting of N, O, and S substituted with 0-1 R^5 ;

20

- R^{4b} , at each occurrence, is selected from H, =O, $(CH_2)_rOR^3$, F, Cl, Br, I, C_{1-4} alkyl, -CN, NO_2 , $(CH_2)_rNR^3R^{3a}$, $(CH_2)_rC(O)R^3$, $(CH_2)_rC(O)OR^{3c}$, $NR^3C(O)R^{3a}$, $C(O)NR^3R^{3a}$, $NR^3C(O)NR^3R^{3a}$, $CH(=NR^3)NR^3R^{3a}$, $NR^3C(=NR^3)NR^3R^{3a}$, $SO_2NR^3R^{3a}$, $NR^3SO_2NR^3R^{3a}$, $NR^3SO_2-C_{1-4}$ alkyl, $NR^3SO_2CF_3$, NR^3SO_2 -phenyl, $S(O)_pCF_3$, $S(O)_p-C_{1-4}$ alkyl, $S(O)_p$ -phenyl, and $(CF_2)_rCF_3$;
- 25

- R^5 , at each occurrence, is selected from CF_3 , C_{1-6} alkyl, phenyl substituted with 0-2 R^6 , and benzyl substituted with 0-2 R^6 ;
- 30

- R^6 , at each occurrence, is selected from H, OH, $(CH_2)_rOR^2$, halo, C_{1-4} alkyl, CN, NO_2 , $(CH_2)_rNR^2R^{2a}$, $(CH_2)_rC(O)R^{2b}$, $NR^2C(O)R^{2b}$, $NR^2C(O)NR^2R^{2a}$, $CH(=NH)NH_2$, $NHC(=NH)NH_2$, $SO_2NR^2R^{2a}$, $NR^2SO_2NR^2R^{2a}$, and $NR^2SO_2C_{1-4}$ alkyl;
- 35

R⁷, at each occurrence, is selected from H, OH, C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₄ alkoxycarbonyl, (CH₂)_n-phenyl, C₆₋₁₀ aryloxy, C₆₋₁₀ aryloxycarbonyl, C₆₋₁₀ arylmethylcarbonyl, C₁₋₄ alkylcarbonyloxy C₁₋₄ alkoxy-
5 carbonyl, C₆₋₁₀ arylcarbonyloxy C₁₋₄ alkoxy carbonyl, C₁₋₆ alkylaminocarbonyl, phenylaminocarbonyl, and phenyl C₁₋₄ alkoxycarbonyl;

10 R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and (CH₂)_n-phenyl;

alternatively, R⁷ and R⁸ combine to form a 5 or 6 membered saturated, ring which contains from 0-1 additional heteroatoms selected from the group consisting of N, O,
15 and S;

R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and (CH₂)_n-phenyl;

20 n, at each occurrence, is selected from 0, 1, 2, and 3;

m, at each occurrence, is selected from 0, 1, and 2;

25 p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, and 3;

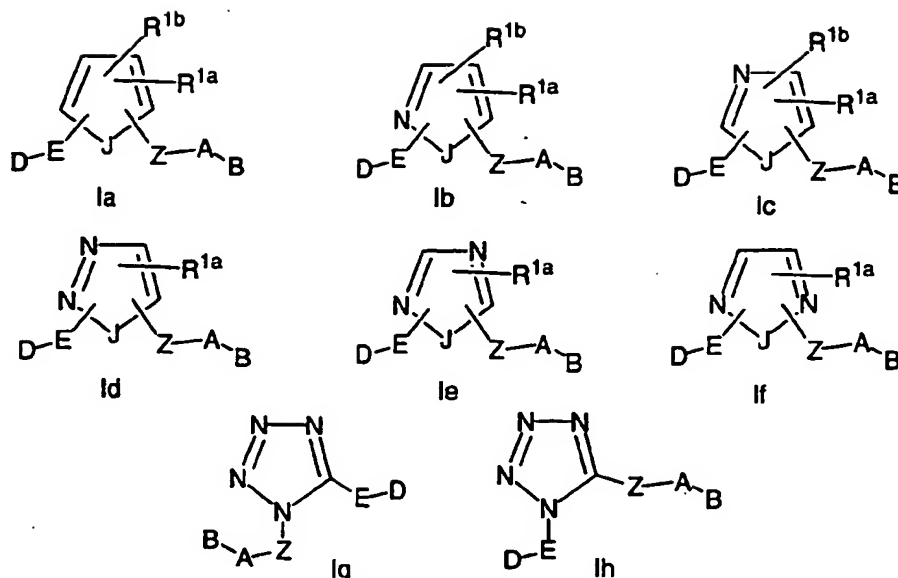
s, at each occurrence, is selected from 0, 1, and 2; and,

30 t, at each occurrence, is selected from 0, 1, 2, and 3;

provided that D-E-G-(CH₂)_s- and -Z-A-B are not both benzamidines.

35

2. A compound according to Claim 1, wherein the compound is of formulae Ia-Ih:



wherein, groups D-E- and -Z-A-B are attached to adjacent atoms on the ring;

- 5 R is selected from H, Cl, F, Br, I, (CH₂)_tOR³, C₁₋₄ alkyl, OCF₃, CF₃, C(O)NR⁷R⁸, and (CR⁸R⁹)_tNR⁷R⁸;
- Z is selected from a CH₂O, OCH₂, CH₂NH, NHCH₂, C(O), CH₂C(O), C(O)CH₂, NHC(O), C(O)NH, CH₂S(O)₂, S(O)₂(CH₂), SO₂NH, and
- 10 NHSO₂, provided that Z does not form a N-N, N-O, NCH₂N, or NCH₂O bond with ring M or group A;
- A is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R⁴;
- 15 phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,
- 20 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl,
- 25 benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

B is selected from: Y, X-Y, NR^2R^{2a} , $\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$, and $\text{NR}^2\text{C}(=\text{NR}^2)\text{NR}^2\text{R}^{2a}$;

5 X is selected from C_{1-4} alkylene, $-\text{C}(\text{O})-$, $-\text{C}(=\text{NR})-$, $-\text{CR}^2(\text{NR}^2\text{R}^{2a})-$, $-\text{C}(\text{O})\text{CR}^2\text{R}^{2a}-$, $-\text{CR}^2\text{R}^{2a}\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^2-$, $-\text{NR}^2\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^2\text{CR}^2\text{R}^{2a}-$, $-\text{NR}^2\text{C}(\text{O})\text{CR}^2\text{R}^{2a}-$, $-\text{CR}^2\text{R}^{2a}\text{C}(\text{O})\text{NR}^2-$, $-\text{CR}^2\text{R}^{2a}\text{NR}^2\text{C}(\text{O})-$, $-\text{NR}^2\text{C}(\text{O})\text{NR}^2-$, $-\text{NR}^2-$, $-\text{NR}^2\text{CR}^2\text{R}^{2a}-$, $-\text{CR}^2\text{R}^{2a}\text{NR}^2-$, O, $-\text{CR}^2\text{R}^{2a}\text{O}-$, and $-\text{OCR}^2\text{R}^{2a}-$;

10

Y is NR^2R^{2a} , provided that X-Y do not form a N-N or O-N bond;

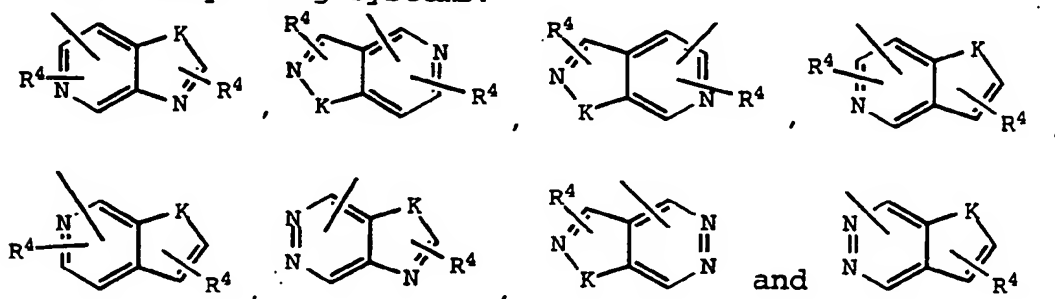
alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a} ;

15

cyclopropyl, cyclopentyl, cyclohexyl, phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, benzofuranyl, benzothiofuranyl, indolyl, benzimidazolyl, benzoxazolyl, benzthiazolyl, indazolyl, benzisoxazolyl, benzisothiazolyl, and isoindazolyl;

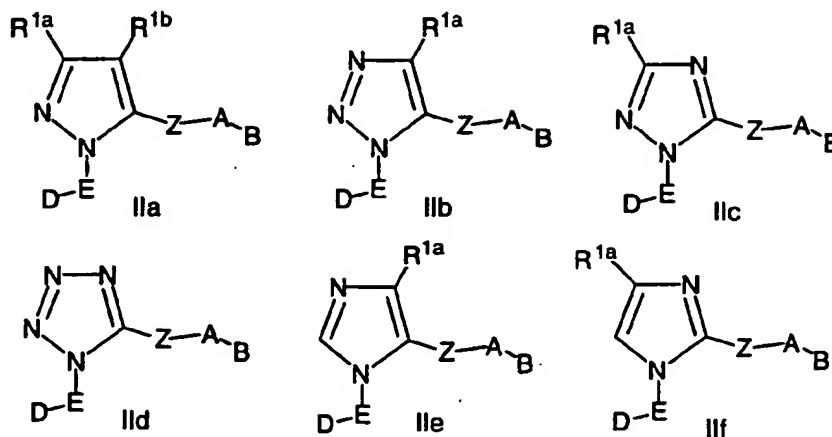
25

30 alternatively, Y is selected from the following bicyclic heteroaryl ring systems:



K is selected from O, S, NH, and N.

- 5 3. A compound according to Claim 2, wherein the compound is of formulae IIa-IIf:



10 wherein;

Z is selected from a C(O), CH₂C(O), C(O)CH₂, NHC(O), C(O)NH, C(O)N(CH₃), CH₂S(O)₂, S(O)₂(CH₂), SO₂NH, and NHSO₂,
provided that Z does not form a N-N or NCH₂N bond with
15 ring M or group A.

4. A compound according to Claim 3, wherein;

20 E is phenyl substituted with R or 2-pyridyl substituted with R;

D is selected from NH₂, NHCH₃, CH₂NH₂, CH₂NHCH₃, CH(CH₃)NH₂, and C(CH₃)₂NH₂, provided that D is substituted ortho to ring M
25 on E; and,

R is selected from H, OCH₃, Cl, and F.

5. A compound according to Claim 4, wherein;

D-E is selected from 2-aminophenyl, 2-methylaminophenyl, 2-aminomethylphenyl, 4-methoxy-2-aminophenyl, 4-methoxy-2-(methylamino)phenyl, 4-methoxy-2-aminomethylphenyl, 4-methoxy-2-(methylaminomethyl)phenyl, 4-methoxy-2-(1-aminoethyl)phenyl, 4-methoxy-2-(2-amino-2-propyl)phenyl, 4-Cl-2-aminophenyl, 4-Cl-2-(methylamino)phenyl, 4-Cl-2-aminomethylphenyl, 4-Cl-2-(methylaminomethyl)phenyl, 4-Cl-2-(1-aminoethyl)phenyl, 4-Cl-2-(2-amino-2-propyl)phenyl, 4-F-2-aminophenyl, 4-F-2-(methylamino)phenyl, 4-F-2-aminomethylphenyl, 4-F-2-(methylaminomethyl)phenyl, 4-F-2-(1-aminoethyl)phenyl, and 4-F-2-(2-amino-2-propyl)phenyl.

6. A compound according to Claim 3, wherein;

Z is C(O)CH₂ and CONH, provided that Z does not form a N-N bond with group A;

A is selected from phenyl, pyridyl, and pyrimidyl, and is substituted with 0-2 R⁴; and,

B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R^{4a};

R⁴, at each occurrence, is selected from OH, (CH₂)_rOR², halo, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, and (CF₂)_rCF₃;

R^{4a} is selected from C₁₋₄ alkyl, CF₃, S(O)_pR⁵, SO₂NR²R^{2a}, and 1-CF₃-tetrazol-2-yl;

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

X is CH₂ or C(O); and,

Y is selected from pyrrolidino and morpholino.

5 7. A compound according to Claim 6, wherein;

A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl,
2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-
10 phenyl, 2-methylphenyl, 2-aminophenyl, and 2-
methoxyphenyl; and,

B is selected from the group: 2-CF₃-phenyl, 2-
(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 2-
(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-
15 (methylsulfonyl)phenyl, 4-morpholino, 2-(1'-CF₃-tetrazol-
2-yl)phenyl, 4-morpholinocarbonyl, 2-methyl-1-imidazolyl,
5-methyl-1-imidazolyl, 2-methylsulfonyl-1-imidazolyl and,
5-methyl-1,2,3-triazolyl.

20

8. A compound according to Claim 3, wherein;

E is phenyl substituted with R or 2-pyridyl substituted with
R;

25

D is selected from NH₂, NHCH₃, CH₂NH₂, CH₂NHCH₃, CH(CH₃)NH₂, and
C(CH₃)₂NH₂, provided that D is substituted ortho to ring M
on E; and,

30 R is selected from H, OCH₃, Cl, and F;

Z is C(O)CH₂ and CONH, provided that Z does not form a N-N bond
with group A;

35 A is selected from phenyl, pyridyl, and pyrimidyl, and is
substituted with 0-2 R⁴; and,

B is selected from X-Y, phenyl, pyrrolidino, morpholino, 1,2,3-triazolyl, and imidazolyl, and is substituted with 0-1 R^{4a};

5 R⁴, at each occurrence, is selected from OH, (CH₂)_rOR², halo, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, and (CF₂)_rCF₃;

R^{4a} is selected from C₁₋₄ alkyl, CF₃, S(O)_pR⁵, SO₂NR²R^{2a}, and 1-CF₃-tetrazol-2-yl;

10

R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl, and benzyl;

X is CH₂ or C(O); and,

15

Y is selected from pyrrolidino and morpholino.

9. A compound according to Claim 8, wherein;

20

D-E is selected from 2-aminophenyl, 2-methylaminophenyl, 2-aminomethylphenyl, 4-methoxy-2-aminophenyl, 4-methoxy-2-(methylamino)phenyl, 4-methoxy-2-aminomethylphenyl, 4-methoxy-2-(methylaminomethyl)phenyl, 4-methoxy-2-(1-aminoethyl)phenyl, 4-methoxy-2-(2-amino-2-propyl)phenyl, 4-Cl-2-aminophenyl, 4-Cl-2-(methylamino)phenyl, 4-Cl-2-aminomethylphenyl, 4-Cl-2-(methylaminomethyl)phenyl, 4-Cl-2-(1-aminoethyl)phenyl, 4-Cl-2-(2-amino-2-propyl)phenyl, 4-F-2-aminophenyl, 4-F-2-(methylamino)phenyl, 4-F-2-aminomethylphenyl, 4-F-2-(methylaminomethyl)phenyl, 4-F-2-(1-aminoethyl)phenyl, and 4-F-2-(2-amino-2-propyl)phenyl;

25

A is selected from the group: phenyl, 2-pyridyl, 3-pyridyl, 2-pyrimidyl, 2-Cl-phenyl, 3-Cl-phenyl, 2-F-phenyl, 3-F-phenyl, 2-methylphenyl, 2-aminophenyl, and 2-methoxyphenyl; and,

30

B is selected from the group: 2-CF₃-phenyl, 2-

(aminosulfonyl)phenyl, 2-(methylaminosulfonyl)phenyl, 2-(dimethylaminosulfonyl)phenyl, 1-pyrrolidinocarbonyl, 2-(methylsulfonyl)phenyl, 4-morpholino, 2-(1'-CF₃-tetrazol-2-yl)phenyl, 4-morpholinocarbonyl, 2-methyl-1-imidazolyl, 5-methyl-1-imidazolyl, 2-methylsulfonyl-1-imidazolyl and, 5-methyl-1,2,3-triazolyl.

10 10. A compound according to Claim 9, wherein the compound is of formula IIa.

15 11. A compound according to Claim 9, wherein the compound is of formula IIb.

20 12. A compound according to Claim 9, wherein the compound is of formula IIc.

25 13. A compound according to Claim 9, wherein the compound is of formula IID.

30 14. A compound according to Claim 9, wherein the compound is of formula IIe.

35 15. A compound according to Claim 9, wherein the compound is of formula IIIf.

 16. A compound according to Claim 3, wherein;

D is selected from -CN, C(=NR⁸)NR⁷R⁹, C(O)NR⁷R⁸, NR⁷R⁸, and CH₂NR⁷R⁸, provided that D is substituted ortho to ring M on E;

E is phenyl substituted with R or pyridyl substituted with R;

R is selected from H, Cl, F, OR³, CH₃, CH₂CH₃, OCF₃, CF₃, NR⁷R⁸,
5 and CH₂NR⁷R⁸;

Z is selected from C(O), CH₂C(O), C(O)CH₂, NHC(O), and C(O)NH,
provided that Z does not form a N-N bond with ring M or
group A;

10

R^{1a} and R^{1b} are independently absent or selected from
-(CH₂)_r-R^{1'}, NCH₂R^{1''}, OCH₂R^{1''}, SCH₂R^{1''}, N(CH₂)₂(CH₂)_tR^{1'},
O(CH₂)₂(CH₂)_tR^{1'}, and S(CH₂)₂(CH₂)_tR^{1'}, or combined to form
a 5-8 membered saturated, partially saturated or
15 unsaturated ring substituted with 0-2 R⁴ and which
contains from 0-2 heteroatoms selected from the group
consisting of N, O, and S;

R^{1'}, at each occurrence, is selected from H, C₁₋₃ alkyl, halo,
20 (CF₂)_rCF₃, OR², NR²R^{2a}, C(O)R^{2c}, (CF₂)_rCO₂R^{2c}, S(O)_pR^{2b},
NR²(CH₂)_rOR², NR²C(O)R^{2b}, NR²C(O)₂R^{2b}, C(O)NR²R^{2a},
SO₂NR²R^{2a}, and NR²SO₂R^{2b};

A is selected from one of the following carbocyclic and
25 heterocyclic systems which are substituted with 0-2 R⁴;
phenyl, piperidinyl, piperazinyl, pyridyl,
pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,
pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl,
isothiazolyl, pyrazolyl, and imidazolyl;

30

B is selected from: Y, X-Y, NR²R^{2a}, C(=NR²)NR²R^{2a}, and
NR²C(=NR²)NR²R^{2a};

X is selected from CH₂, -CR²(CR²R^{2b})(CH₂)_t-, -C(O)-, -C(=NR)-,
35 -CH(NR²R^{2a})-, -C(O)NR²-, -NR²C(O)-, -NR²C(O)NR²-, -NR²-,
and O;

Y is NR²R^{2a}, provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following carbocyclic and heterocyclic systems which are substituted with 0-2 R^{4a};

- 5 phenyl, piperidinyl, piperazinyl, pyridyl, pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl, pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl, thiazolyl, isothiazolyl, pyrazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, and 1,3,4-triazolyl;
- 15 R⁴, at each occurrence, is selected from =O, OH, Cl, F, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2b}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, CH(=NH)NH₂, NHC(=NH)NH₂, SO₂NR²R^{2a}, NR²SO₂-C₁₋₄ alkyl, NR²SO₂R⁵, S(O)_pR⁵, and (CF₂)_rCF₃;
- 20 R^{4a}, at each occurrence, is selected from =O, OH, Cl, F, C₁₋₄ alkyl, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2b}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, CH(=NH)NH₂, NHC(=NH)NH₂, SO₂NR²R^{2a}, NR²SO₂-C₁₋₄ alkyl, NR²SO₂R⁵, S(O)_pR⁵, (CF₂)_rCF₃, and 1-CF₃-tetrazol-2-yl;
- 25 R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl substituted with 0-2 R⁶, and benzyl substituted with 0-2 R⁶;
- 30 R⁶, at each occurrence, is selected from H, =O, OH, OR², Cl, F, CH₃, CN, NO₂, (CH₂)_rNR²R^{2a}, (CH₂)_rC(O)R^{2b}, NR²C(O)R^{2b}, CH(=NH)NH₂, NHC(=NH)NH₂, and SO₂NR²R^{2a};
- 35 R⁷, at each occurrence, is selected from H, OH, C₁₋₆ alkyl, C₁₋₆ alkylcarbonyl, C₁₋₆ alkoxy, C₁₋₄ alkoxycarbonyl, benzyl, C₆₋₁₀ aryloxy, C₆₋₁₀ aryloxycarbonyl, C₆₋₁₀ arylmethylcarbonyl, C₁₋₄ alkylcarbonyloxy C₁₋₄ alkoxycarbonyl, C₆₋₁₀ arylcarbonyloxy C₁₋₄ alkoxycarbonyl,

C₁₋₆ alkylaminocarbonyl, phenylaminocarbonyl, and phenyl
C₁₋₄ alkoxy carbonyl;

5 R⁸, at each occurrence, is selected from H, C₁₋₆ alkyl and
benzyl; and

alternatively, R⁷ and R⁸ combine to form a morpholino group;
and,

10 R⁹, at each occurrence, is selected from H, C₁₋₆ alkyl and
benzyl.

15 17. A compound according to Claim 16, wherein;

E is phenyl substituted with R or 2-pyridyl substituted with
R;

20 R is selected from H, Cl, F, OCH₃, CH₃, OCF₃, CF₃, NH₂, and
CH₂NH₂;

Z is selected from a C(O)CH₂ and C(O)NH, provided that Z does
not form a N-N bond with group A;

25 R^{1a} is selected from H, CH₃, CH₂CH₃, Cl, F, CF₃, OCH₃, NR²R^{2a},
S(O)_pR^{2b}, CH₂S(O)_pR^{2b}, CH₂NR²S(O)_pR^{2b}, C(O)R^{2c}, CH₂C(O)R^{2c},
C(O)NR²R^{2a}, and SO₂NR²R^{2a};

30 R^{1b} is selected from H, CH₃, CH₂CH₃, Cl, F, CF₃, OCH₃, NR²R^{2a},
S(O)_pR^{2b}, CH₂S(O)_pR^{2b}, CH₂NR²S(O)_pR^{2b}, C(O)R^{2c}, CH₂C(O)R^{2c},
C(O)NR²R^{2a}, and SO₂NR²R^{2a};

A is selected from one of the following carbocyclic and
heterocyclic systems which are substituted with 0-2 R⁴;
35 phenyl, pyridyl, pyrimidyl, furanyl, thiophenyl,
pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl,
pyrazolyl, and imidazolyl;

B is selected from: Y and X-Y;

X is selected from CH_2 , $-\text{CR}^2(\text{CR}^2\text{R}^{2b})-$, $-\text{C}(\text{O})-$, $-\text{C}(=\text{NR})-$,
5 $-\text{CH}(\text{NR}^2\text{R}^{2a})-$, $-\text{C}(\text{O})\text{NR}^2-$, $-\text{NR}^2\text{C}(\text{O})-$, $-\text{NR}^2\text{C}(\text{O})\text{NR}^2-$, $-\text{NR}^2-$,
and O;

Y is NR^2R^{2a} , provided that X-Y do not form a N-N or O-N bond;

alternatively, Y is selected from one of the following
10 carbocyclic and heterocyclic systems which are
substituted with 0-2 R^{4a} ;
phenyl, piperidinyl, piperazinyl, pyridyl,
pyrimidyl, furanyl, morpholinyl, thiophenyl, pyrrolyl,
pyrrolidinyl, oxazolyl, isoxazolyl, isoxazolinyl,
15 thiazolyl, isothiazolyl, pyrazolyl, imidazolyl,
oxadiazolyl, thiadiazolyl, triazolyl, 1,2,3-oxadiazolyl,
1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl,
1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl,
1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl,
20 1,2,4-triazolyl, 1,2,5-triazolyl, and 1,3,4-triazolyl;

R^2 , at each occurrence, is selected from H, CF_3 , CH_3 , benzyl,
and phenyl;

25 R^{2a} , at each occurrence, is selected from H, CF_3 , CH_3 , benzyl,
and phenyl;

R^{2b} , at each occurrence, is selected from CF_3 , OCH_3 , CH_3 ,
benzyl, and phenyl;

30 R^{2c} , at each occurrence, is selected from CF_3 , OH, OCH_3 , CH_3 ,
benzyl, and phenyl;

alternatively, R^2 and R^{2a} combine to form a 5 or 6 membered
35 saturated, partially unsaturated, or unsaturated ring
which contains from 0-1 additional heteroatoms selected
from the group consisting of N, O, and S;

R³, at each occurrence, is selected from H, CH₃, CH₂CH₃, and phenyl;

5 R^{3a}, at each occurrence, is selected from H, CH₃, CH₂CH₃, and phenyl;

R⁴, at each occurrence, is selected from OH, Cl, F, CH₃, CH₂CH₃, NR²R^{2a}, CH₂NR²R^{2a}, C(O)R^{2b}, NR²C(O)R^{2b}, C(O)NR²R^{2a}, and CF₃;

10

R^{4a}, at each occurrence, is selected from OH, Cl, F, CH₃, CH₂CH₃, NR²R^{2a}, CH₂NR²R^{2a}, C(O)R^{2b}, C(O)NR²R^{2a}, SO₂NR²R^{2a}, S(O)_pR⁵, CF₃, and 1-CF₃-tetrazol-2-yl;

15 R⁵, at each occurrence, is selected from CF₃, C₁₋₆ alkyl, phenyl substituted with 0-2 R⁶, and benzyl substituted with 1 R⁶;

20 R⁶, at each occurrence, is selected from H, OH, OCH₃, Cl, F, CH₃, CN, NO₂, NR²R^{2a}, CH₂NR²R^{2a}, and SO₂NR²R^{2a};

R⁷, at each occurrence, is selected from H and C₁₋₃ alkyl;

25 R⁸, at each occurrence, is selected from H, CH₃, and benzyl;

25

R⁹, at each occurrence, is selected from H, CH₃, and benzyl; and,

30 t, at each occurrence, is selected from 0 and 1.

30

18. A compound according to Claim 17, wherein;

35 D is selected from NR⁷R⁸, and CH₂NR⁷R⁸, provided that D is substituted ortho to ring M on E;

- R^{1a} is absent or is selected from H, CH_3 , CH_2CH_3 , Cl, F, CF_3 , OCH_3 , NR^2R^{2a} , $S(O)_pR^{2b}$, $C(O)NR^2R^{2a}$, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2c}$, $CH_2C(O)R^{2c}$, and $SO_2NR^2R^{2a}$;
- 5 R^{1b} is absent or is selected from H, CH_3 , CH_2CH_3 , Cl, F, CF_3 , OCH_3 , NR^2R^{2a} , $S(O)_pR^{2b}$, $C(O)NR^2R^{2a}$, $CH_2S(O)_pR^{2b}$, $CH_2NR^2S(O)_pR^{2b}$, $C(O)R^{2b}$, $CH_2C(O)R^{2b}$, and $SO_2NR^2R^{2a}$;
- A is selected from one of the following carbocyclic and
10 heterocyclic systems which are substituted with 0-2 R^4 ;
phenyl, pyridyl, and pyrimidyl;
- B is selected from: Y and X-Y;
- 15 X is selected from $-C(O)-$ and O;
- Y is NR^2R^{2a} , provided that X-Y do not form a O-N bond;
- alternatively, Y is selected from one of the following
20 carbocyclic and heterocyclic systems which are
substituted with 0-2 R^{4a} ;
phenyl, piperazinyl, pyridyl, pyrimidyl,
morpholinyl, pyrrolidinyl, imidazolyl, and 1,2,3-
triazolyl;
- 25 R^2 , at each occurrence, is selected from H, CF_3 , CH_3 , benzyl,
and phenyl;
- R^{2a} , at each occurrence, is selected from H, CF_3 , CH_3 , benzyl,
30 and phenyl;
- R^{2b} , at each occurrence, is selected from CF_3 , OCH_3 , CH_3 ,
benzyl, and phenyl;
- 35 R^{2c} , at each occurrence, is selected from CF_3 , OH, OCH_3 , CH_3 ,
benzyl, and phenyl;

alternatively, R² and R^{2a} combine to form a ring system
selected from pyrrolidinyl, piperazinyl and morpholino;

5 R⁴, at each occurrence, is selected from Cl, F, CH₃, NR²R^{2a},
and CF₃;

R^{4a}, at each occurrence, is selected from Cl, F, CH₃,
SO₂NR²R^{2a}, S(O)_pR⁵, and CF₃;

10 R⁵, at each occurrence, is selected from CF₃ and CH₃;

R⁷, at each occurrence, is selected from H, CH₃, and CH₂CH₃;
and,

15 R⁸, at each occurrence, is selected from H and CH₃.

19. A compound according to Claim 1, wherein the
compound is selected from:

20 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-
(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;

25 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-
(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;

30 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-
pyrazole-5-(N-(2'-sulfamido-[1,1']-biphen-4-
yl))carboxamide;

3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-
pyrazole-5-(N-(2'-sulfamido-[1,1']-biphen-4-
yl))carboxamide;

35 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-
5-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;

40 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-
1H-pyrazole-5-(N-(2'-sulfamido-[1,1']-biphen-4-
yl))carboxamide;

3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-
(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;

45 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-
(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;

- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 5 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 10 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 15 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 20 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 25 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 30 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 35 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 40 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 45 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 50 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 55 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;

- 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-
1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-
biphen-4-yl)) carboxyamide;
- 5 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-
(4-(1-pyrrolidinocarbonyl)phenyl) carboxyamide;
- 10 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-
(1-pyrrolidinocarbonyl)phenyl) carboxyamide;
- 15 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-
pyrazole-5-(N-(4-(1-
pyrrolidinocarbonyl)phenyl) carboxyamide;
- 20 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-
pyrazole-5-(N-(4-(1-
pyrrolidinocarbonyl)phenyl) carboxyamide;
- 25 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-
5-(N-(4-(1-pyrrolidinocarbonyl)phenyl) carboxyamide;
- 30 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-
1H-pyrazole-5-(N-(4-(1-
pyrrolidinocarbonyl)phenyl) carboxyamide;
- 35 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-
(2-fluoro-4-(1-pyrrolidinocarbonyl)phenyl) carboxyamide;
- 40 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-
fluoro-4-(1-pyrrolidinocarbonyl)phenyl) carboxyamide;
- 45 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-
pyrazole-5-(N-(2-fluoro-4-(1-
pyrrolidinocarbonyl)phenyl) carboxyamide;
- 50 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-
(5-((2-sulfamido)phenyl)pyridin-2-yl) carboxyamide;
- 55 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-
(2-sulfamido)phenyl)pyridin-2-yl) carboxyamide;
- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-
pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyridin-2-
yl) carboxyamide;

- 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyridin-2-yl)carboxamide;
5
- 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyridin-2-yl)carboxamide;
- 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyridin-2-yl)carboxamide;
10
- 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyridin-2-yl)carboxamide;
15
- 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyridin-2-yl)carboxamide;
- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyridin-2-yl)carboxamide;
20
- 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyridin-2-yl)carboxamide;
25
- 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyridin-2-yl)carboxamide;
30
- 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyridin-2-yl)carboxamide;
- 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyrimidin-2-yl)carboxamide;
35
- 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyrimidin-2-yl)carboxamide;
40
- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyrimidin-2-yl)carboxamide;
- 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyrimidin-2-yl)carboxamide;
45
- 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyrimidin-2-yl)carboxamide;
50
- 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-sulfamido)phenyl)pyrimidin-2-yl)carboxamide;
55

- 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyrimidin-2-yl)carboxamide;
- 5 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2-methylsulphonyl)phenyl)pyrimidin-2-yl)carboxamide;
- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyrimidin-2-yl)carboxamide;
- 10
- 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyrimidin-2-yl)carboxamide;
- 15
- 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyrimidin-2-yl)carboxamide;
- 20
- 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-((2-methylsulphonyl)phenyl)pyrimidin-2-yl)carboxamide;
- 25
- 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 30
- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 35
- 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 40
- 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 45
- 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 50
- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;

- 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 5 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 10 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 15 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 20 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 25 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 30 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((2-methyl)imidazo-1-yl)phenyl)carboxamide;
- 35 3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 3-Ethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 40 3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 45 3-Methyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 3-Ethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((5-methyl)imidazo-1-yl)phenyl)carboxamide; and,
- 50 3-Trifluoromethyl-1-(2-N-methylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2-fluoro-4-((5-methyl)imidazo-1-yl)phenyl)carboxamide;
- 55 and pharmaceutically acceptable salts thereof.

20. A compound according to Claim 1, wherein the compound is selected from:

- 5
3-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 10
5-Methyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-3-(N-(2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 15
3-Methyl-1-(2-N,N-dimethylaminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-N-methylsulfamido-[1,1']-biphen-4-yl))carboxamide;
- 20
3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1]-biphen-4-yl))carboxamide;
- 25
3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-methylsulfonyl-[1,1]-biphen-4-yl))carboxamide;
- 30
3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(2'-sulfamido-[1,1]-biphen-4-yl))carboxamide;
- 35
3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(4-N-pyrrolidinocarbonyl)phenyl)carboxamide;
- 40
N-Benzylsulfonyl-4-(3-trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxamido)piperidine;
- 45
3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(2'-sulfonamido)phenyl)pyrid-2-yl)carboxamide;
- 50
3-Trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-(N-(5-(pyrid-2-yl))pyrid-2-yl)carboxamide;
- N-Benzyl-4-(3-trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxamido)piperidine;
- N-Phenylsulfonyl-4-(3-trifluoromethyl-1-(2-aminomethyl-4-methoxyphenyl)-1H-pyrazole-5-carboxamido)piperidine;
- 3-Trifluoromethyl-1-(2-aminomethyl-4-chlorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;

- 3-Trifluoromethyl-1-(2-aminomethyl-4-chlorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 5 3-Trifluoromethyl-1-(2-aminomethyl-5-chlorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 10 3-Trifluoromethyl-1-(2-aminomethyl-4-chlorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 15 3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 20 3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 25 3-Trifluoromethyl-1-(2-aminomethyl-5-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 30 3-Trifluoromethyl-1-(2-aminomethyl-5-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 35 3-Trifluoromethyl-1-(2-aminomethyl-4,5-difluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 40 3-Trifluoromethyl-1-(2-aminomethyl-3-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 45 3-Trifluoromethyl-1-(2-aminomethyl-3-fluorophenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 50 3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(4-(2-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 55 3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(4-(2-sulfamido-[1,1']-biphen-4-yl))carboxamide;
- 3-Trifluoromethyl-1-(2-aminomethyl-4-fluorophenyl)-1H-pyrazole-5-(N-(4-(N-(N-(methylsulfonyl)iminol)pyrrolidino)phenyl))carboxamide;

- 3-Trifluoromethyl-1-(2-(N-glycyl)aminomethyl-4-methoxyphenyl)-
1H-pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-
biphen-4-yl))carboxamide;
5
- 3-Trifluoromethyl-1-(2-(N-phenylacetyl)aminomethyl-4-
methoxyphenyl)-1H-pyrazole-5-(N-(3-fluoro-2'-
methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 10 3-(Trifluoromethyl)-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-
(N-(2'-methylsulfonyl-[1,1']-biphen-4-yl))carboxamide;
- 3-Trifluoromethyl-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-
(2'-aminosulfonyl-[1,1']-biphen-4-yl))carboxamide;
15
- 3-Trifluoromethyl-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-
(3-fluoro-2'-aminosulfonyl-[1,1']-biphen-4-
yl))carboxamide;
- 20 3-Trifluoromethyl-1-(2-(aminomethyl)phenyl)-1H-pyrazole-5-(N-
(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-4-
yl))carboxamide;
- 3-Trifluoromethyl-1-(2-(N-(glycyl)aminomethyl)phenyl)-1H-
pyrazole-5-(N-(3-fluoro-2'-methylsulfonyl-[1,1']-biphen-
4-yl))carboxamide;
25
- 3-Trifluoromethyl-1-(2-(N-(N-
methylglycyl)aminomethyl)phenyl)-1H-pyrazole-5-(N-(3-
fluoro-2'-methylsulfonyl-[1,1']-biphen-4-
yl))carboxamide;
30
- 3-Trifluoromethyl-1-(2-carboxamidophenyl)-1H-pyrazole-5-(N-(3-
fluoro-2'-methylsulfonyl-[1,1']-biphen-4-
yl))carboxamide;
35
- 3-Trifluoromethyl-1-(2-cyanophenyl)-1H-pyrazole-5-(N-(3-
fluoro-2'-methylsulfonyl-[1,1']-biphen-4-
yl))carboxamide;
40
- 1-(2'-Aminomethylphenyl)-5-[(2'-methylsulfonyl)-3-fluoro-
[1,1']-biphen-4-yl]aminocarbonyl]-tetrazole;
- 1-(2'-Aminomethylphenyl)-5-[(2'-aminosulfonyl-[1,1']-biphen-4-
yl)aminocarbonyl]-tetrazole;
45
- 1-[2-(Aminomethyl)phenyl]-3-thiomethoxy-5-[(2-fluoro)-(2'-
methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;
- 50 1-[2-(Aminomethyl)phenyl]-3-methylsulfonyl-5-[(2-fluoro)-(2'-
methylsulfonyl-[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;
- 1-[2-(Aminomethyl)phenyl]-5-[(2-fluoro)-(2'-methylsulfonyl-
[1,1']-biphen-4-yl)aminocarbonyl]triazole;
55

1-[2-(Aminomethyl)phenyl]-5-[(2-fluoro)-(2'-methylsulfonyl)-
[1,1']-biphen-4-yl)aminocarbonyl]pyrazole;

5 1-[2-(Aminomethyl)phenyl]-3-trifluoromethyl-5-[((2-fluoro)-
(2'-pyrrolidinomethyl)-[1,1']-biphen-4-
yl)aminocarbonyl]pyrazole; and,

10 1-[2-(Aminomethyl)phenyl]-3-trifluoromethyl-5-[((2-fluoro)-
(2'-hydroxymethyl)-[1,1']-biphen-4-
yl)aminocarbonyl]pyrazole;

and pharmaceutically acceptable salts thereof.

15 21. A pharmaceutical composition, comprising: a
pharmaceutically acceptable carrier and a therapeutically
effective amount of a compound according to Claim 1 or a
pharmaceutically acceptable salt thereof.

20

22. A method for treating or preventing a thromboembolic
disorder, comprising: administering to a patient in need
thereof a therapeutically effective amount of a compound
according to Claim 1 or a pharmaceutically acceptable salt

25 thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/26427

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D231/14 A61K31/415 A61K31/44 A61K31/445 C07D231/24
C07D231/22 C07D249/04 C07D257/04 C07D401/12 C07D401/14
C07D403/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X | EP 0 554 829 A (FUJISAWA PHARMACEUTICAL CO) 11 August 1993 see page 3 - page 3; claims 1-10 see example 1 | 1-22 |
| A | US 5 612 353 A (EWING WILLIAM R ET AL) 18 March 1997 see abstract; claims see column 31 - column 32 see column 13 - column 14; example 1 | 1-22 |
| P, X | WO 98 28269 A (DU PONT MERCK PHARMA) 2 July 1998 see abstract; claims 19-23 see claims | 1-22 |
| | --- -/- | |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

22 April 1999

Date of mailing of the international search report

03/05/1999

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/26427

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| E | WO 98 57937 A (DU PONT MERCK PHARMA) 23 December 1998 see page 251, line 7 - line 30; claim 5 see abstract; claims 2,8,9 ----- | 1-22 |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/26427

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: claim 22
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 22
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☒ Claims Nos.: not applicable
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: not applicable

In view of the extremely broad Markush claims, the search was executed with due regard to the PCT Search Guidelines (PCT/GL/2), C-III, paragraph 2.1, 2.3 read in conjunction with 3.7 and Rule 33.3 PCT, i.e. particular emphasis was put on the inventive concept, as illustrated by claim 3 and claims 19 - 20 of the present application, and by those compounds which were actually prepared and for which physical data was given. The international search was, in so far as possible and reasonable, complete in that it covered the entire subject-matter to which the claims are directed.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter. Application No

PCT/US 98/26427

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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